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AUTHORITY

USAMRMC ltr, dtd 15 May 2003

AD_____

Award Number: DAMD17-99-1-9053

TITLE: Evaluation of Optical Sonography™ for Real-time Breast Imaging and Biopsy Guidance

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REPORT DATE: August 2002

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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12/6/02 _____

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2002	Final (19 Jul 99 - 18 Jul 02)

4. TITLE AND SUBTITLE
Evaluation of Optical Sonography™ for Real-time Breast Imaging and Biopsy Guidance

5. FUNDING NUMBERS
DAMD17-99-1-9053

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (proprietary information, Aug 02). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

12b. DISTRIBUTION CODE

13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

Despite advances in complementary approaches to breast mammography, breast cancer remains a prevalent and devastating disease. Advances fail to provide real-time, large field-of-view, high-resolution approaches to breast imaging where early detection and subsequent management of the disease are primary targets. This study evaluated a promising approach to breast imaging and image guidance using Diffractive Ultrasound (DUS), developed by Advanced Imaging Technologies, Inc.

Systematic methods were developed for evaluating modifications to prototypes aimed at improving DUS image quality and adaptations for breast imaging. Ten normal volunteers and ten from a diagnostic group were studied to resolve procedural aspects of image acquisition, obtain data for a range of breast sizes and types to more fully evaluate the strengths and weaknesses of the technology, examine the robustness of processing algorithms, and establish descriptors for image interpretation.

The study indicates that DUS has strength in differentiating soft tissue structures, particularly in women with dense breast composition, and identifying boundaries where strong diffractive components are present. The simulated biopsy data collected indicate that physicians can be successful in acquiring targets. Results indicate that DUS has a high potential for detecting and differentiating breast lesions and shows promise in providing accurate, real-time biopsy guidance.

14. SUBJECT TERMS	15. NUMBER OF PAGES
breast cancer, diffractive ultrasound, advanced imaging	47
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

Significant progress has been made over the last decade in the detection and diagnosis of breast disease. However, conventional imaging modalities have limitations, and fully satisfactory methods for early detection of breast cancer have not yet been identified. X-ray mammography is currently the primary imaging technique for the detection and diagnosis of breast disease. But, mammographers miss about 10 to 15% of all cancers, particularly those in patients with dense breast composition.[1] The National Alliance of Breast Cancer Organizations (NABCO) reports the false positive rate at about 15% and the false negative rate from 10 to 15%.[2] Conventional ultrasound is the adjunctive diagnostic imaging technique of choice. It has been demonstrated to be highly accurate at identifying cystic structures, one class of benign lesions, but it is not recommended for screening. In addition, reflective ultrasound is very operator dependent and lacks a global image in which suspicious regions are compared to normal tissues. Optical Sonography* or Diffractive Ultrasound (DUS) has shown promise in detection of breast lesions and in differentiating soft tissues non-invasively.

The DUS technique incorporates many of the advantages of other imaging modalities. For example, DUS utilizes real-time imaging similar to conventional ultrasound, an advantage over mammography; it has higher spatial resolution than conventional ultrasound at typical operating frequencies; it requires minimum operator dependency to generate high quality images; it generates a larger field of view than conventional ultrasound, similar to X-ray, but without the ionizing radiation exposure; it uses an automated collection of multiple slices similar to MRI (magnetic resonance imaging) and CT (computed tomography); and among other image quality strengths has inherent enhanced edges of soft tissue structures, yielding information important to diagnosis. The *primary objective* of this study was to evaluate the suitability of DUS for the detection and characterization of breast disease.

Major accomplishments during the three year study included: the evaluation of prototype components and system level performance which drove further developments; development of a standardized metrics program; proven procedures for collecting image data; the data collection and evaluation of normals and symptomatic volunteers; completion of a feasibility study investigating the use of this device for real-time breast biopsy; evaluation of applied image processing tools, and the generation of a catalog of descriptors for use in image interpretation and communication.

BODY

Diffractive Ultrasound (DUS) utilizes "through wave" and acoustical holographic techniques to gather detailed image information about the body segment being examined. DUS is categorized as a unique imaging modality because of its non-traditional use of sound. While conventional ultrasound relies on the reflective properties of sound and is a pulsed wave technique, DUS takes advantage of the diffractive properties of sound. This technique produces high-contrast, high-resolution images from soft tissue structures such as the breast.

Breast imaging has been first application of DUS in clinical studies.[3-5] The Avera, the first application of Diffractive Ultrasound, has been cleared as a general imaging device by U.S. The

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* While the term "Optical Sonography" will remain in the title of this project, Advanced Imaging Technologies, Inc. (AIT) has adopted the new term, Diffractive Ultrasound (DUS) as more descriptive of the technology's strengths. Input from physicians, scientists and marketing consultants has been fundamental to this decision.

Food and Drug Administration (FDA) through the 510k submission process. Cleared applications include breast imaging, breast lesion measurement and breast biopsies. Other indications for DUS include pediatric, vascular and musculoskeletal imaging. A more detailed review of the science and history of this technology is provided in the literature.[6-13]

The *purpose and scope* of this study are provided by year. In *Year 1* efforts were undertaken to alter a prototype system in preparation for breast imaging, and to develop methods for evaluating these system changes and the resultant images. In addition, various procedures for breast imaging were tested and methods for image enhancement were explored. The scope in *Year 2* was to implement the methods developed during Year 1. This included the implementation of formalized system metrics and breast imaging procedures, along with preliminary image enhancement efforts. The results of data collected from a group of individuals with normal breast anatomy, along with preliminary results from simulated breast biopsies completed on biopsy training phantoms were presented. In *Year 3,* the scope was to implement methods developed during the detection and characterization studies of Year 1 and refined in Year 2. During Year 3, symptomatic volunteers with confirmed masses were imaged and several new post processing scheme were evaluated. Comparisons were made with mammographic and reflective ultrasound images, and pathology was used as "truth." The relative sensitivity of the device was determined on a larger data set and a catalog of descriptors was established.

Review of Progress - Years 1 and 2

A synopsis of Year 1 and Year 2 results are provided. The reader is referred to the 2000 and 2002 Annual Reports for more detail. Tasks conducted in Year 3 are provided in more detail.

System Modifications: During Years 1 and 2 several component and system level modifications to the alpha and beta prototype (Figures 1 and 2) were made as a result of evaluations conducted during this study. Many of these advancements were reported in the 2001 Annual Report. Subsequent evaluations underscored several important issues. First, the rotational feature provided access to the breast from any position in a 200 plus degree arc about the breast. But, it also increased the system footprint unrealistically, hindering installation in a typically- sized medical imaging room. And, in fact, the newer prototype (Figure 2) could not be installed at the University of Washington, our consultant's site, due to room size limitations. While reducing the footprint was possible, the true revelation was that a system producing image slices much like a CT scanner has all the necessary volumetric data inherent in the image set. In other words, there would be image information redundancy in sets of image slices acquired at various rotational positions. The decision was made to eliminate the rotation feature. In addition to reducing the overall system footprint, the proposed medial-lateral imaging approach increased access to the patient chest wall by lowering the patient between the source transducer housing and the lens tube. In previous designs the patient had to lay over the transducer housing and acoustic lens tube in the cranial-caudal position, thus reducing the ability to lower the patient into the water bath and sound beam. The pre-production design concept is shown in Figure 3. This design was implemented and in Year 3 the pre-production unit was built, and quality tested in house. Evaluation of this unit occurred as part of this study. Subsequent UL testing was completed and several systems were manufactured as a first commercial product. This working system was displayed at RSNA and is shown in Figure 4.

In additional to improvements outlined in the 2000 and 2001 Annual Reports, a new Graphical User Interface developed as a separate effort was completed and incorporated. This software created the DICOM compatible formats for seamless integration with both the AIT review stations for image review and post processing, and the Radiology information networks at hospitals and clinics.

The new software was designed to address several image acquisition challenges uncovered in assessments on this program. One concern was the time necessary to acquire and archive an autoscan. The tendency for a woman to move during the autoscan increased with the increase in time to acquire and archive an image set. In addition, while Year 2 studies determined that respiration did not adversely degrade images if those respirations were small, the probability that motion would be detected increased with scan time. The new software addresses this issue by reducing the time to acquire and save an autoscan by more than half (approximately 30 seconds for a 20 slice image set).

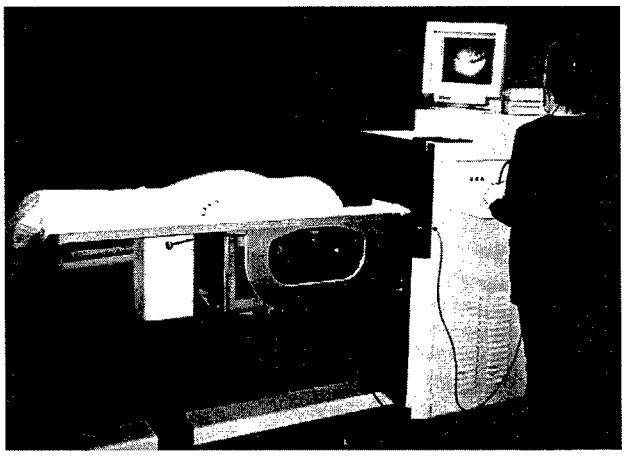


Figure 1. Alpha prototype designed specifically for breast imaging.

Figure 2. Beta prototype used for study data collection.

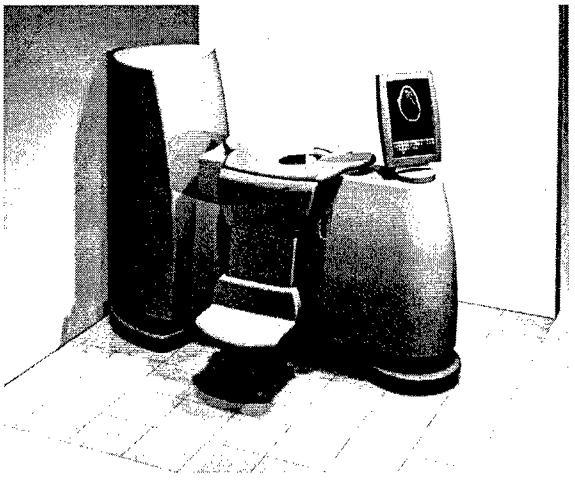


Figure 3. Pre-production unit design

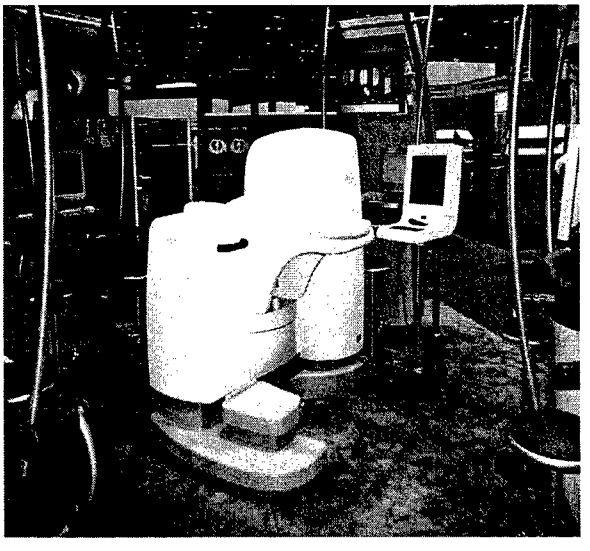


Figure 4. Avera breast imaging system displayed at RSNA 2001 in Chicago IL.

Another practical issue addressed during Year 3 related to bubble formation in the patient tank waterbath when using pressurized inlet tap water. The size of the patient imaging tank was reduced from about 33 gallons to about 2.5 gallons, reducing dramatically the water used and sent to drain. However, the concern relative to image degradation from bubble formation still remained. This issue was resolved by the installation of a small vacuum pump/degasser.

Images are now being acquired using the Avera, but it should be noted that this device was not available for patient imaging until recently and the images presented in this study are taken from a predecessor device discussed in the Year 2 Annual Report.

Clarification of Reviewer Technical Questions

Several questions were raised as a part of the August 2001 Annual Report. These are addressed as follows:

1. From the figures provided in the report, the question was whether the view is limited to the medial-lateral direction. The device is limited to a medial-lateral view only, with about ±11 degrees of rotation. The key to this design revision was presented in the 2001 Annual Report. The realization was that because this system presents slice data much like CT, there is volumetric data inherent in the image set. The intent in the future will be to use the image slices to generate volumetric data sets so that the reviewer can view from any direction and generate cross-sectional data at any located as desired. In the interim a location graphic is provided in the GUI to orient the reviewer to superior, inferior, anterior and posterior breast as well as the slice location of the displayed image.
2. It was not clear that the patient interface could be used from either side of the device. The patient table can be installed on either side of the device, but must be specified upon installation. The sound energy does pass in one direction, but slices can be acquired either from medial to lateral, or lateral to medial or as a still image or series of still images at any desired location(s) within the breast. Images are rotated and flipped as appropriate for export to the image review station. Initial assessment was that images should be rotated to mimic standard mammography presentation, and that has been accomplished.
3. The concern was also versed regarding a single side approach for biopsy. The table is positioned high enough that the physician can sit on a low stool and perform biopsy from either side (i.e., needle entry from either a cranial or caudal approach). The biopsy windows drop down on both sides after the water is drained for biopsy. The patient table rotation feature allows for repositioning to improve lesion access as necessary. This must be done prior to draining the patient tank in order to preserve sound continuity.

In addition, Year 1 produced phantoms for evaluating system performance, tests for assessing image quality, evaluation of the practical issues affecting image quality, preliminary image processing algorithms, data base development and image evaluation forms.

In Year 2, major accomplishments included continual development of phantoms, measurement tools, and procedures that provided a standard and repeatable method to evaluate image quality. The attached publication outlines the results of this effort.[14] Methods and procedures for collecting breast images consistently were developed and have been adopted by AIT as Test Procedure 02003-01. Collection and evaluation of breast images for volunteers with normal breast anatomy was completed and images were post-processed using a variety of algorithms which were being incorporated as the AIT Advanced Post-processing Tool Concept. The measurement feature was validated and cleared through the FDA 510K submission process. Images were presented illustrating this feature in the Year 2 Annual Report. And finally, DUS underwent evaluation as a potential guided biopsy device. Results from this latter study were published and are attached.[15]

Review of Progress - Year 3

Completion of remaining Tasks 13-17 occurred during Year 3. Progress on each of these tasks will be discussed in order.

Task 13: Recruit symptomatic volunteers with confirmed breast masses, perform DUS and conventional breast sonography.

Ten symptomatic volunteers were recruited for the study per outlined protocols. Clinical work-up included the collection of subject medical reports, images from mammography, conventional ultrasound and Diffractive Ultrasound, and associated pathology reports. Image review sessions were conducted with Radiologists and evaluation sheets were completed for each imaging modality. The intent of the evaluation sessions was to correlate lesion findings among modalities and identify characteristics for each modality that were reproducible and predictive of clinical outcome. In the case of mammography, the American College of Radiology 5-point assessment system was used. For Diffractive Ultrasound, discussion focused on a trial set of descriptive characteristics that became the focus for a catalog of descriptors that is discussed in Task 17 (and attached as a draft white paper).

Task 14: Perform review of images by each observer and apply image processing techniques.

Images were reviewed and comparisons among mammograms, reflective ultrasound and diffractive ultrasound images were made. Pathology was used as "truth" data. Data were obtained from medical records, radiology reports and evaluation sheets completed by physicians upon case reviews.

In addition to image processing algorithms evaluated and implemented in Year 2, several additional evaluations were completed in Year 3. These focused on issues uncovered in Year 1 and 2 that were directly linked to improving image quality. Areas addressed included background uniformity, image artifacts and lesion visibility. Synthetic flat fielding, Z averaging and gamma curve alterations were applied to each best image slice selected during initial reviews by scientists and physicians. In each case an original slice from the autoscan was reviewed along with 6 processed images of the identical slice. The processing algorithm combinations are shown in Table 1.

Table 1. Image Processing algorithms evaluated in Year 3

Process 1	synthetic flat fielding at Gamma = 0.6
Process 2	synthetic flat fielding at Gamma = 1
Process 3	synthetic flat fielding + Z-Averaging at Gamma = 0.6
Process 4	synthetic flat fielding + Z-Averaging at Gamma = 1
Process 5	Z-Averaging at Gamma = 0.6
Process 6	Z-Averaging at Gamma = 1

The synthetic flat-fielding was accomplished by sampling a number of background points from a background image and creating a synthetic (thus, "noise-free") background by fitting a surface through those points. Z-averaging was accomplished by averaging a number of consecutive slices (3-4) where it was assumed that lesions would appear consistently in more than one slice, therefore averaging consecutive slices would enhance lesions and reduce background noise. Evaluation of the original images and images incorporating the processing algorithms were completed as part of Task 15.

Task 15: Measure region of interest data on masses, normal breast structures and evaluate contrast, optimum frequency bandwidth for raw and processed images, analyze raw and processed images and correlate with available and measure tissue property data.

The measurement feature on the system was implemented and tested by three operators as part of Year 2 efforts and was reported in the Year 2 Annual Report. Each operator was trained in taking linear measurements and then asked to take 5 different measurements on a target that was positioned in the field of view. The five measurements were repeated 3 times in varying orders. Each operator was able to repeat each linear measurement to within 1.2% of actual dimension with the exception of one measurement where the operator interpreted the measurement endpoints incorrectly, resulting in a 3.5% error. The most experienced operator averaged to within 0.5% of actual dimensions with the most inexperienced operator averaging 1.7% from actual (including the data from the misinterpreted target endpoint scenario). The measurement feature was subsequently cleared via the FDA 510K submission process. An example image with measurement feature implemented is shown in Figure 5.

Figure 5. Example DUS image illustrating measurement feature

The processed images discussed in Task 14 were evaluated by 2 Radiologists and one Medical Physicist. Table 2 presents the image comparison results and pathology data. Data evaluating the original and processed images were generated for each of the 10 volunteers reviewed. Included was an overall image quality rating, using a scale from 1 to 5. Also a subjective assessment at to whether the applied processing algorithm (1 to 6 shown above) had "improved" the image quality from a diagnostic perspective, whether the image quality had remained the "same," or whether the algorithm had made the image quality "worse." A set of example imaged is provided in Figures 6 though 12, and illustrate the original image along with changes reflecting processes 1 through 6 described in Table 1. In general, images where contrast was increased provided better edge definition and structure visibility, and were judged to be better in overall image quality. Heavily smoothed or dark images consistently rated lower on the overall image quality score. The specific areas of lesion visibility, background uniformity and image artifacts were assessed independently and a summary is included below.

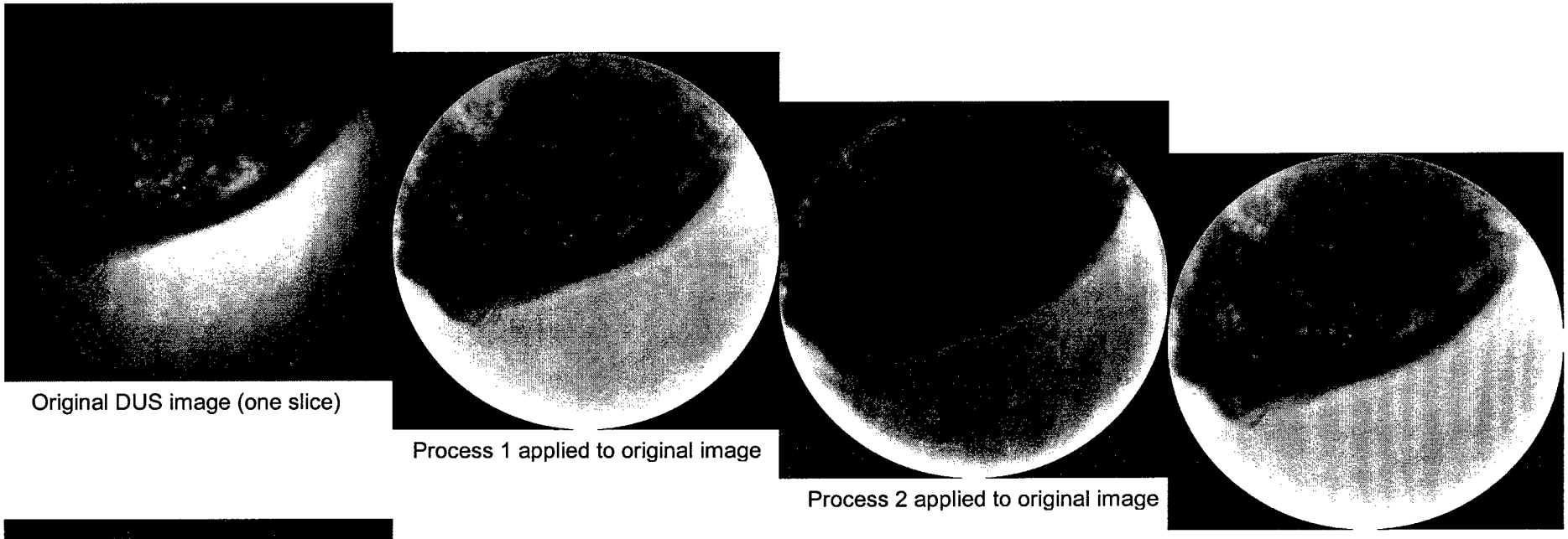
<u>Lesion Visibility</u>

- Images of higher contrast than the original image consistently scored higher on lesion visibility. The higher contrast made it easier to delineate the boundaries of structures. However, some concern was expressed that the higher contrast could mean a loss of information in other areas of the breast. It was suggested that an "edge enhancement" algorithm that would preserve the dynamic range throughout the image while providing the boundary delineation of the higher contrast image would be a better solution.

Table 2. Image Comparison for 10 Symptomatic Volunteers

Lesion #	Age	Breast Comp	Lesion Type	Seen on Scr Mammo	Screening Mammo Assessment	Seen on Diag Mammo	Diagnostic Mammo Assessment	Seen on RUS	RUS Assessment	Seen on DUS	DUS Assessment	Pathology
1	49	2	Solid - Benign	TRUE	Other studies/ information needed	FALSE		FALSE	Negative	TRUE	Suspicious	fibrocystic change, apocrine metaplasia
2	69	3	Solid - Benign	FALSE		TRUE	Suspicious	TRUE	Suspicious	TRUE	Suspicious	scar calcifications
3	52	3	Solid - Benign	FALSE		TRUE	Suspicious	TRUE	Suspicious	FALSE	Negative	fibroadenoma
4	52	2	Cystic - Simple	TRUE	Other studies/ information needed	TRUE	Other studies/ information needed	TRUE	Benign Finding	TRUE	Suspicious	no biopsy
5	62	2	Cystic - Simple	TRUE	Other studies/ information needed	TRUE	Other studies/ information needed	TRUE	Suspicious	TRUE	Suspicious	ruptured cyst, inflammation scarring
6	47	2	Cystic - Simple	TRUE	Other studies/ information needed	TRUE	Other studies/ information needed	TRUE	Suspicious	TRUE	Benign Finding	multiple cysts, milk of calcium
7	74	3	Solid - malignant	TRUE	Other studies/information needed	FALSE		TRUE	Highly Suspicious	TRUE	Suspicious	infiltrating ductal carcinoma
8	42	3	Cystic - Complex	FALSE		FALSE	Negative	TRUE	Suspicious	FALSE	Negative	complex cysts, aspirated
9	78	2	Solid - malignant	TRUE	Other studies/ information needed	TRUE	Other studies/ information needed	TRUE	Suspicious	TRUE	Suspicious	intraductal carcinoma
10	49	3	Solid - Benign	TRUE	Other studies/ information needed	TRUE	Other studies/ information needed	TRUE	Suspicious	TRUE	Suspicious	fibroadenoma

Figures 6 through 12. Example of an image set evaluated illustrating original image slice and 6 processed images using algorithm combinations defined in Table1

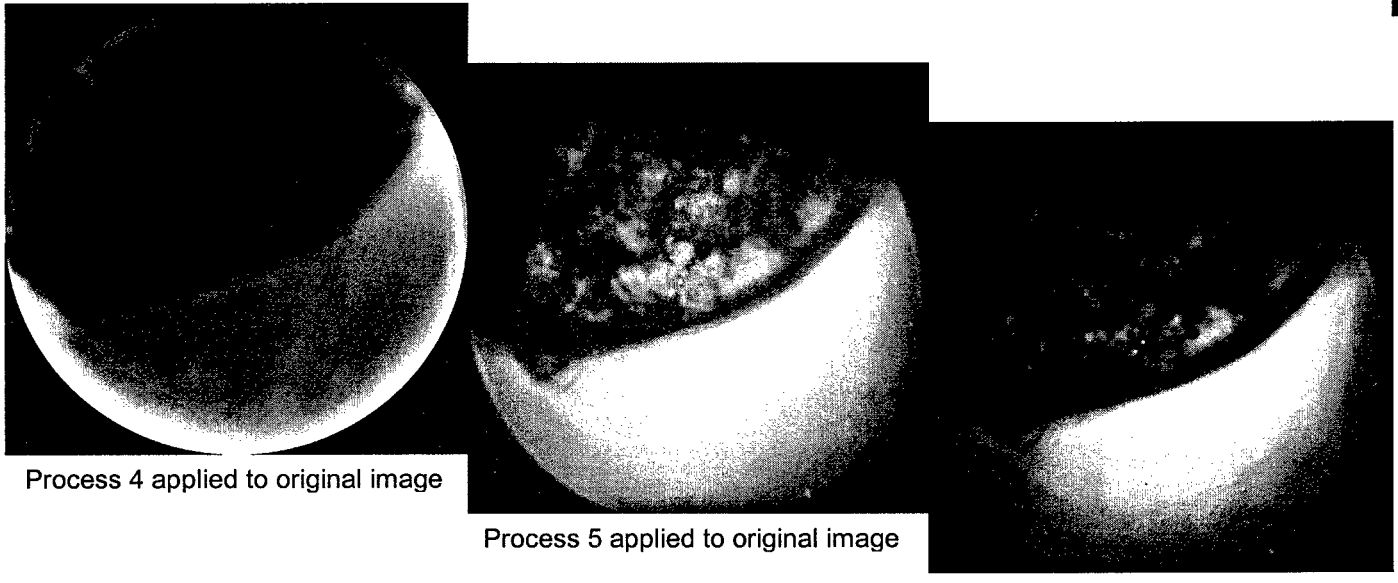


Original DUS image (one slice)

Process 1 applied to original image

Process 2 applied to original image

Process 3 applied to original image



Process 4 applied to original image

Process 5 applied to original image

Process 6 applied to original image

Background Uniformity

- In terms of evaluating background uniformity, the images that decreased the central "area of saturation" and improved the overall central uniformity were looked at positively while images that increased the central "area of saturation" were deemed to be unacceptable.
- In the images that improved the overall central uniformity, a bright "halo" appearance consistently appeared in the periphery and was labeled a "non-uniformity" artifact. This peripheral halo did not impair the readers' abilities to assess tissue and would easily be addressed in a clinical training session as a consistent but harmless artifact. This halo was more apparent in smaller breasted women where the breast did not fill the entire FOV.
- In smaller breasted women, inconsistencies in the background uniformity were more apparent in the central zone of the FOV in particular; a dark spot could be easily seen in the center. This spot was not apparent in larger breasted women presumably because hidden by breast tissue. Evaluators did raise a concern that this could interfere with accurate interpretation of image.

Artifacts

- Artifacts were not deemed to be an issue in this evaluation. There were 2 consistent artifacts that were described:
  - An artifact that occurred to the right of the image in the field of view (FOV) that was described as alternating black/white stripes, appearing as transducer diffraction lines. These did not obscure tissue or cause problems with image interpretation and could be easily dealt with in clinical training for operators.
  - In the bottom third of the image, 2 small dark regions were consistently seen in the background. These did not affect image interpretation when they fell outside of the breast area, but may affect the images in a larger breast and should be eliminated.

Overall improvements that were especially noted included image sharpness and increased field of view as compared to the previous normal cases reviewed in Year 2. Several decisions relating to image processing were made as a result of image evaluations in Years 1 through 3. Averaging schemes, frequency sweeping, transducer rotation, and gamma curves have been optimized and incorporated. Presets will be developed to control frequency combinations, initial windowing and leveling, and intensities to deal with variations in breast composition. The operator will be given controls to alter these default presets and controls for window and leveling at the acquisition system. Additional processing features will be provided at the AIT review workstation. The development of image processing algorithms and evaluations will be an ongoing exercise.

The optimum frequency bandwidth was explored, with the thought that controlling both high and low frequencies and selectively compounding frequencies might yield improved images. Given that AIT transducers are manufactured as one up devices, each transducer is tuned individually and frequency bandwidth is dependent on intrinsic resonance of the material along with developed matching layers and impedance backing. Within these constraints, single frequency and sweep frequency images were acquired. Averaging of single frequencies did not yield better images than current sweep techniques employed at this time. Further transducer development and investigation will be required.

The images obtained from symptomatic subjects were evaluated based upon knowledge of tissue property data collected in Year 1.[16-25] While little can be determined with any high level

of certainly due to the small size of the data set, generally the denser malignant structures that show higher attenuation appear as darker in DUS images. As an example, Calderon et al.[16] found significantly different ranges of attenuation for various tissue pathology. Figure 13 shows good correlation between high attenuation and malignancy, except in sample 108 (a medullary carcinoma). Other studies cited difficulty in viewing medullary carcinomas at these frequency ranges also. It is hypothesized that their microscopic structure (more homogeneous) lacks the fibrous tissue that proliferates in other cancers and consequently there is less ultrasonic absorption and scattering. Using these data and the sound velocity data for malignant and benign tissue,[20,21] one can calculate the approximate attenuation per dB for both for malignant tissue (22dB/cm at 2.5 MHz- removing the medullary carcinoma case) and benign tissue (9.8 dB/cm). This information may imply that DUS could expect to have an advantage when imaging malignant tissues, due to higher spatial resolutions at the lower operating frequencies implemented to date. Benign tissues would be expected to appear as less attenuative and lighter in grayscale compared to malignant tissue, and somewhat darker than surrounding normal tissue. This tendency has proven to be generally true and is illustrated in Figures14 and 15.

Histological Classification of Samples

Tissue	Sample Number
Normal	102, 109
Fibrocystic Disease	103, 105, 107, 110, 113, 114, 125
Carcinomatous Changes:	
Infiltrating Ductal Carcinoma	104, 106, 111, 115, 121, 124
Intraductal Carcinoma	101
Scirrhous Carcinoma	122
Medullary Carcinoma	108

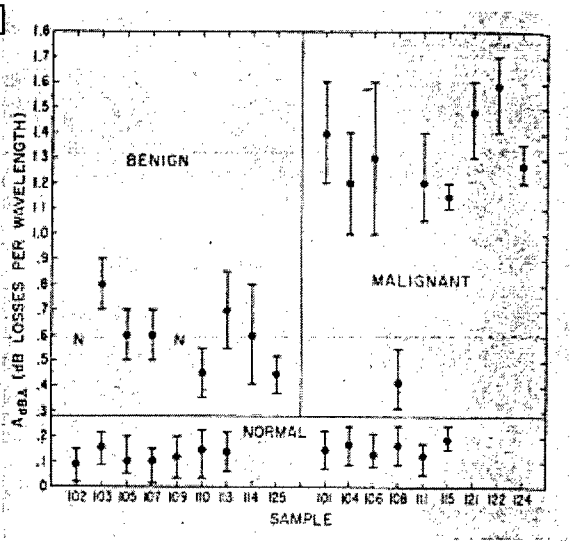


FIGURE 5. The ultrasonic attenuation per wavelength versus tissue pathology. Table I lists the histological analysis of the samples. The attenuation per wavelength $A_{dB/\lambda}$ is defined as loss in decibels per wavelength of tissue path. For an explanation of the error bars, see text.

Figure 13. Table illustrating ultrasonic attenuation for breast tissue pathology[16]

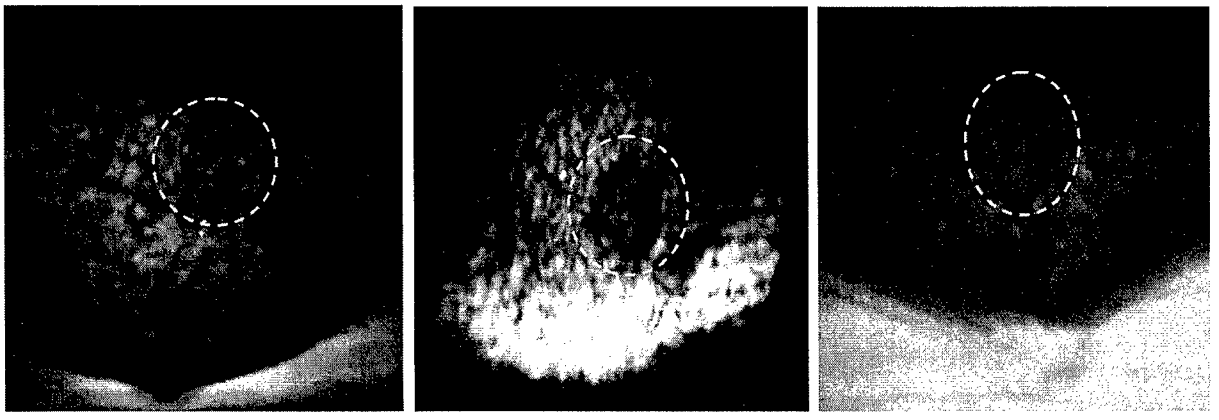


Figure 14. Fibroadenomas shown in three different women. Frame A shows a 2.0 cm oval mass located in the middle breast of a predominantly fatty breast of a 47 year old female. Margins are partially circumscribed with septations present. Frame B shows an oval shaped mass in a 40 year old female with heterogeneously dense breast composition. Frame C shows an oval mass with indistinct margins in a heterogeneously dense breast of a 37 year old female.

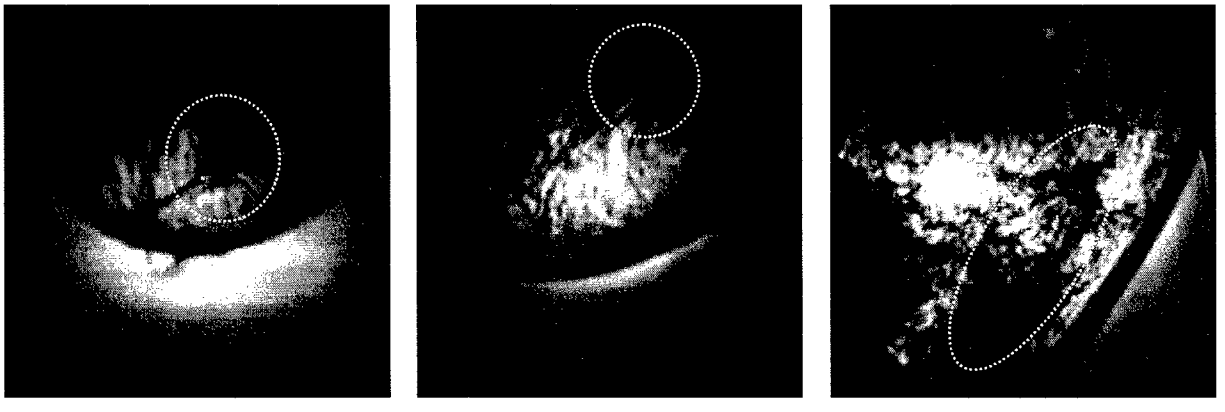


Figure 15. Three malignant solid masses in three different women. Frame A shows an adenocarcinoma in a 56 year old female. Frame B shows an infiltrating ductal carcinoma in the upper outer quadrant of a 73 year old female. Frame C shows an invasive adenocarcinoma with lobular and ductal features in a 64 year old female. All three cases show heterogeneously dense breast composition.

Task 16: Compute relative sensitivity of DUS, X-ray mammography and conventional sonography.

It was not reasonable to determine relative sensitivity based upon the small data set collected in this study. Consequently, data sets were assessed from several studies combined. This review discusses clinical data obtained from two partner sites, Virginia Mason Medical Center (VMMC) in Seattle, WA and Johns Hopkins Medical Institute (JHMI) in Baltimore, MD. The 10 symptomatic cases from this study were also included. The protocols implemented at both institutions were designed as pilot studies. These preliminary studies provided technical and clinical experience, and image data necessary to evaluate initial imaging procedures, image quality and image interpretation.

Preliminary clinical results included 144 patients in the pilot studies. Within that study group, 155 total lesions were analyzed, comparing mammography, conventional ultrasound and DUS, and using pathology results, when available, as "truth." Overall, there were 61 solid lesions (14

malignant, 47 benign) and 71 cysts. The remaining 23 patients had negative findings, implying no mass was detected on any imaging modality and, if performed, biopsy results were negative. Preliminary DUS study results demonstrated an advantage over mammography and ultrasound in detecting solid lesions overall (DUS: 89%, mammography: 84%, conventional ultrasound: 84%). When used in conjunction with mammography as an adjunctive diagnostic tool, DUS demonstrated a sensitivity of 93% for diagnosis of malignant lesions, which is a significant advantage over mammography alone (79%) and equal to conventional ultrasound. The specificity of DUS was slightly less than conventional ultrasound, 72% vs. 77%, as was the positive predictive value (PPV), 25% vs. 28%. The negative predictive value (NPV) was the same for both DUS and conventional ultrasound (99%).

It should be noted that experience in characterizing solid lesions using DUS was limited with the current study population including only 14 malignant masses and 47 benign solid masses. Although the ability to detect solid lesions is high, radiologists reviewing the DUS studies cannot yet be considered expert users and currently tend to err on the side of caution during review, labeling most solid masses as "suspicious." This results in a high false positive rate, impacting both specificity and PPV for DUS. Once radiologists have gained more experience with DUS, their ability to differentiate between solid malignant and solid benign lesions will likely improve, reducing the false positive rate.

Task 17: Develop catalog of descriptors by all observers in conference.
The catalog of descriptors developed as part of this task was generated with input from physicians and technologists after image reviews completed in Year 2 and 3. It is anticipated that this effort will be the foundation for image interpretation and training in the future. The results of this task are presented as a draft White Paper attached to this report.[26]

KEY RESEARCH ACCOMPLISHMENTS

- System characterization and optimization
- Development of standardized and repeatable tools and methods to evaluate image quality.
- Collection and evaluation of images from normal volunteers and volunteers with confirmed malignant and benign lesions.
- Evaluation and implementation of image processing tools.
- Evaluation of DUS as an image guidance technology for breast imaging.
- Evaluation of the relative sensitivity of DUS as compared to X-ray mammography and reflective ultrasound
- Development of a catalog of descriptors

REPORTABLE OUTCOMES

Poster presentation: XXVI International Acoustical Imaging Symposium in Ontario, Canada (Sept 9-12, 2001)

Paper presentation and SPIE Proceedings publication: Fecht, B.A. and P.S. Jensen, "Toward Guided Breast Biopsy using Diffractive Energy Imaging," Proc. SPIE International Symposium on Medical Imaging 2002, International Society for Optical Engineering, San Diego, CA (2002).

Paper presentation and SPIE Proceedings publication: Garlick, T.F., B.A. Fecht, J.O. Shelby, V.I. Neeley, "Metrics Program for Assessing Diffractive Energy Imaging System Performance," Proc. SPIE International Symposium on Medical Imaging 2002, International Society for Optical Engineering, San Diego, CA (2002).

Internal AIT White Paper for future publication: Fecht, B.A. "Diffractive Ultrasound Descriptors for Breast Imaging; a guide to image interpretation," Internal AIT White Paper (Draft), July 2002.

CONCLUSIONS

The results of this study have had a major impact on the characterization and advancement of the DUS technology. The development of procedures to determine quantitatively the quality and effectiveness of the DUS imaging process (from hardware and software development to imaging procedures) is viewed as a key accomplishment in the development of DUS utility and value.

Standardized metric procedures provided value during not only the study, but will continue to provide value to future system developments. An integral part of this key accomplishment was the assessment and implementation of options for storage and retrieval of images for both process evaluations as well as for use in image evaluation and enhancement.

Imaging normal and symptomatic volunteers provided input regarding skin coupling, physical comfort, patient movement, water temperature, compression, and system settings. Results were formalized as part of a breast imaging procedure. The final key accomplishment under this category was the successful implementation of a GUI-based Image Processing tool which will allow the operator to record his or her post-processing settings helping to build a database of post processing parameters to optimize performance.

Another promising accomplishment was in the progress toward evaluating and establishing the DUS Imager as an effective imaging tool for guiding surgical biopsies. Measurement features were tested and proved successful in the biopsy of simulated breast targets. AIT believes that biopsy guidance will become an important application for this device.

Sensitivity data show the strength and promise of this technology first as an adjunct tool but with additional development as a potential screening device for early detection of breast cancer. The development of the first catalog of descriptors will assist in image interpretation as this technology grows to meet the needs of the medical community.

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APPENDICES

1. List of Personnel Receiving Pay on Project

Principal Investigator: Patrick S. Jensen, Ph.D.
Former Principal Investigator: George F. Garlick, Ph.D.
Investigator; Barbara A. Fecht
Investigator: Ronald L. Shelby
Investigator: Jerod O. Shelby
Investigator: Todd F. Garlick
Investigator: Dyan Blaize-Richards

2. Attached Documents

Garlick, T.F., B.A. Fecht, J.O. Shelby, V.I. Neeley, "Metrics Program for Assessing Diffractive Energy Imaging System Performance," Proc. SPIE International Symposium on Medical Imaging 2002, International Society for Optical Engineering, San Diego, CA (2002).

Fecht, B.A. and P.S. Jensen, "Toward Guided Breast Biopsy using Diffractive Energy Imaging," Proc. SPIE International Symposium on Medical Imaging 2002, International Society for Optical Engineering, San Diego, CA (2002).

Fecht, B.A. "Diffractive Ultrasound Descriptors for Breast Imaging; a guide to image interpretation," Internal AIT White Paper (Draft), July 2002.

Metrics program for assessing Diffractive Energy Imaging system performance

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ABSTRACT

A standardized metrics program was developed and implemented by Advanced Diagnostics, Inc. (ADI) to quantify Diffractive Energy Imaging (DEI) system performance. DEI is a medical imaging technology which uses primarily diffracted wave information obtained from passing ultrasound energy through the anatomy. The resulting real-time, large field-of-view, high-resolution images are currently undergoing clinical evaluation for detection and management of breast disease. This unique imaging modality required novel modifications to conventional measurement and evaluation tools. Measurement tools were developed and metrics procedures were standardized to ensure measurement accuracy and repeatability during performance testing. The system modulation transfer function, effective size of the field-of-view, spatial resolution across the effective field-of-view, contrast resolution, minimum detection, and field uniformity were quantified. Improved system metrics monitor improvements to DEI image quality and are supported through images of target standards and subjective validation using images of human anatomy.

Keywords: Diffractive Energy Imaging, acoustical holography, transmission ultrasound, system performance

1. INTRODUCTION

The goal at Advanced Diagnostics, Inc. (ADI) was to develop and implement a metrics program which would provide an analytical definition of DEI image quality and the ability to track changes to the quality of images. Six metrics were identified as important to achieving this goal. These included: system modulation transfer function (MTF), effective size of the field-of-view, spatial resolution across the effective field-of-view, contrast resolution, minimum detection, and field uniformity. Methodologies utilized and the principle advantages and disadvantages of each metric are discussed, along with a description of the targets developed for use in completing measurements.

2. METHODOLOGY

The ADI metrics program was applied to the performance evaluation of Diffractive Energy Imaging (DEI) systems. DEI is a dynamic, real-time imaging technology that uses the principles of acoustical holography to produce unique images of the human anatomy. The ADI technology is being evaluated at several clinical sites to appraise its potential to detect and characterize breast disease. Several cases have been presented in the literature.[1]

2.1 Technology Description

DEI images are generated by first passing coherent ultrasound through a body segment. The ultrasonic energy is absorbed, reflected, diffracted and refracted by anatomical structures within the body, thus perturbing the transmitted wave in a manner unique to the internal anatomy itself. A pair of acoustic lenses selectively projects information emanating from a single slice (focal plane) within the object onto a detector. Adjustments in the position of these acoustic lenses permits repositioning of the focal plane anywhere within the targeted anatomical volume and permits acoustic magnification in selected regions of interest. The summation of the perturbations in the transmitted wave is combined with a reference wave in real-time to generate the acoustic hologram. Information contained within the hologram is converted back into a two-dimensional image by illuminating the hologram with coherent light and viewing

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it with a digital camera. Three-dimensional data sets can be constructed by acquiring images at sequential focal planes and reassembling them using volumetric reconstruction.

Because DEI is a through-transmission ultrasound imaging technology based on forward diffraction captured on a plane wavefront, the resulting images are significantly different than those generated using reflective mode ultrasound. A detailed review of the science and history of DEI and acoustical holography is provided in the literature.[2-7]

2.2 Approach

The goal of the ADI metrics program was to establish a method for assessing performance at the system level. In order to control optimum configuration during system development and to evaluate accurately different system configurations, it was imperative that a baseline metric be established. For this reason, metrics were performed on a standard configuration before making changes to the system and performing subsequent evaluations. This required not only maintaining a standard component configuration but maintaining identical operating parameters as well. These parameters included acoustic intensity, focus, magnification, frames averaged, and frequency range.

The approach to image quality improvement relied primarily on the ability to improve the critical imaging chain components. When a component had undergone a change that was expected to improve image quality, several metrics were performed. First, component bench testing was completed. Second, the improved component was installed within the imaging chain and system metrics were performed. By comparing the change in metrics, potential influence of particular components on the overall image quality was determined. This approach to metrics also provided valuable data to develop more accurate analytical models of the DEI imaging chain. Reliable metrics were key to performance improvement and tracking system stability.

3. RESULTS

The metrics developed to track image quality improvements during system modifications, to track system drift over time, and to characterize system performance are described.

3.1 System MTF

The system modulation transfer function (MTF) has been used extensively in the field of optics to characterize film, lenses, printers, and monitors, and was adapted easily to characterize DEI performance and track image quality changes. It proved to be a useful tool that integrated both contrast and spatial resolution to evaluate image sharpness. One principle advantage of the MTF is its distributive properties, indicative of its usefulness as a measurement technique to evaluate individual component performance. As an example, when the system MTF and the MTF of the optical subsystem are known, a straightforward calculation will yield the MTF of the acoustical subsystem. This is illustrated in Equation 1. This approach can be further broken down to evaluate components within each subsystem (cameras, lenses, detectors, etc.), which supports the improvement philosophy outlined above.

$$\mathcal{H}_{acoustics}(f_n) = \frac{\mathcal{H}_{system}(f_n)}{\mathcal{H}_{optics}(f_n)} \qquad \text{where, } \mathcal{H} = \text{MTF and f = frequency} \qquad (1)$$

To obtain the system MTF an analysis of the modulation transfer function of a resultant image was required. Many targets were evaluated as a basis for calculating the system MTF (e.g., various line and point targets). A step response target, often referred to as a knife-edge, was chosen due to the ease of fabrication, repeatability and relative ruggedness as compared to most line targets. The knife edge target was fabricated and positioned in the patient imaging tank to obtain an image for evaluation. A standard image analysis algorithm used the knife-edge image and a perpendicular bisecting routine to compute a resulting MTF at three locations along the length of the knife-edge target (Figure 1). When the system MTF was compared to the optical chain MTF it became apparent that the acoustical chain dominated the system MTF (see Figure 2). At a single line frequency of 1.25 line pairs/mm the acoustical imaging chain MTF is 26% compared to the system MTF value of 21.5%. Despite this obvious discrepancy dirty optics and misaligned fixtures

have demonstrated erratic results in the optical chain MTF showing that this can influence the system MTF. When this approach was carried to the acoustical chain components the detector was modeled as optical film, the acoustic lens assembly as an optical lens, and the transducer aperture as an optical lens with zero curvature.

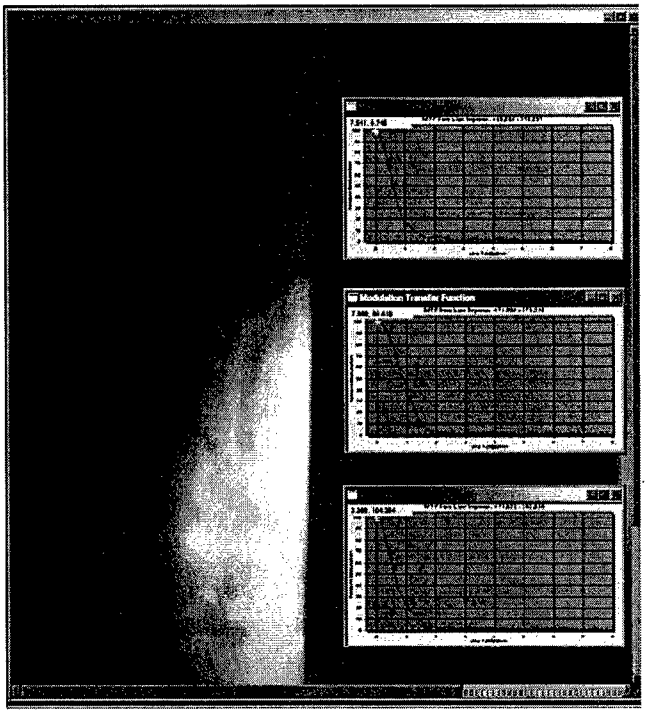

Fig. 1: DEI image of knife-edge target with computed MTF at three locations

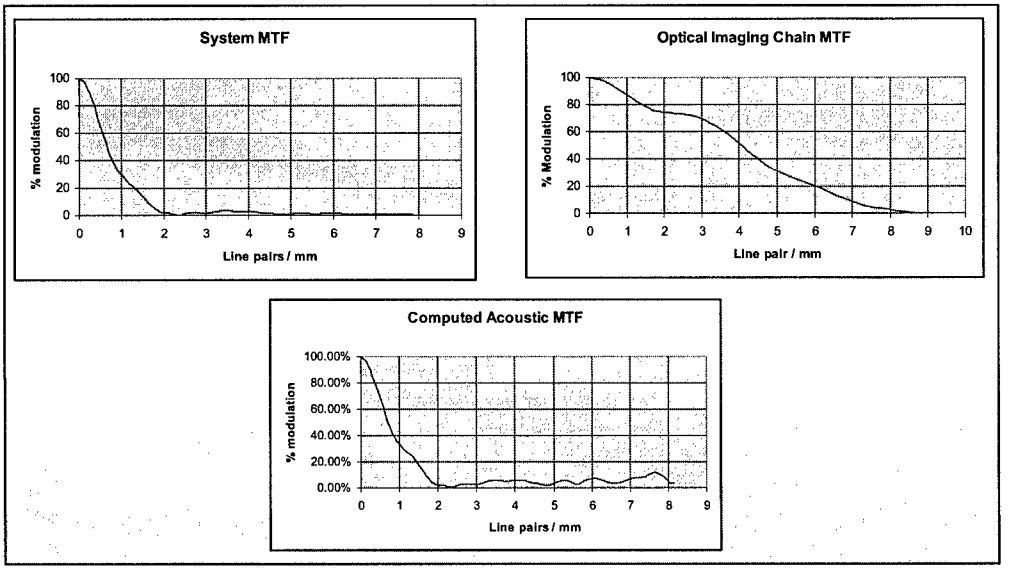

Fig. 2: System and component MTFs

3.2 Effective field-of-view

The effective field-of-view (FOV) is the area illuminated by the source transducers and defined by the FOV target area visible in the image. Unlike the system MTF, this metric was not as easily derived analytically and was very dependent on the geometries and apertures of critical components. More specifically, the detector aperture, camera aperture, transducer aperture, magnification and optical apertures influenced the system effective FOV. Nevertheless, this was an important metric to include in image quality characterization and was the primary means of establishing pixel size and thereby, actual magnification. This metric not only provided a measure of the active image area size, but it also was a measure of relative FOV location with respect to patient position. It was interesting to note that the FOV in the DEI technology was not the same as the effective FOV. Because this technology not only measures the diffracted energy but also detects the absence of sound (e.g., due to reflection, attenuation), the resultant image area was always larger than the effective image area (defined as that region where diffractive energy is detectable). This was established by using an FOV target that had a series of holes with carefully selected diameters that were essentially visible only with the use of diffractive energy.

The field-of-view (FOV) target was a machined cross with a series of 3 mm holes spaced 0.5 cm apart center-to-center, in both vertical and horizontal dimensions (Figure 3). The target was mounted on a stand placed on the bottom of the patient imaging tank at a specified distance from the transducer head. The operator focused on the target and increased the intensity to maximize contrast between the holes and substrate material. The image was captured (Figure 4), the numbers of holes that appear in the FOV were counted and an effective field-of-view was calculated. In recent system enhancements the effective FOV increased from 74.6 cm^2 to 118.8 cm^2.

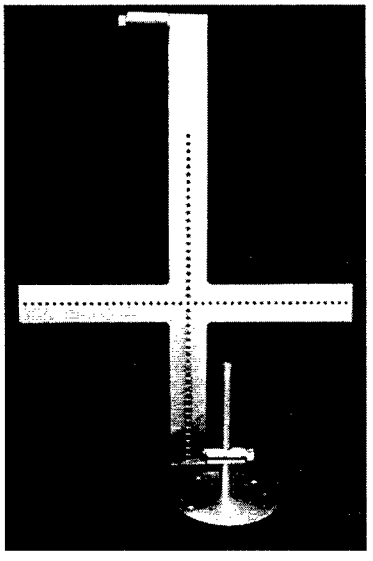

Fig. 3: Field-of-view target

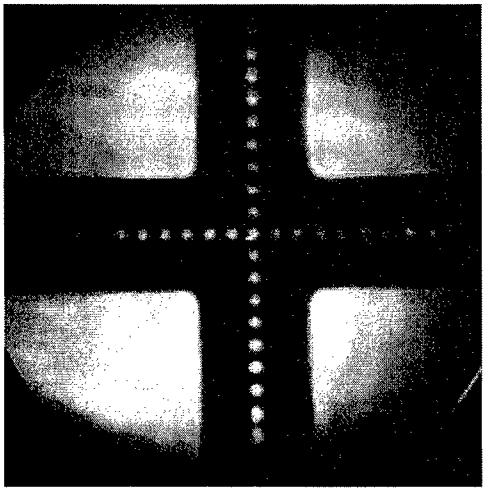

Fig. 4: DEI image of field-of-view target

3.3 Spatial resolution

Spatial resolution is defined as the ability to resolve or separate two objects visually. Although this definition seems straightforward, it is actually a bit arbitrary and has led to the creation of many criteria for quantifying spatial resolution, including the popular Rayleigh criterion. For this reason and other factors, it is not relied on as heavily for analytical assessment and system improvement as is the MTF. Nevertheless, it is a powerful technique for gauging image quality and is readily employed for its ease of use and quick feedback to the operator.

The spatial resolution target standardized for use in ADI metrics was a 6.35 cm by 6.35 cm delron block, 0.64 cm thick (Figure 5). The target had a series of hole pairs machined into the 0.64 cm thickness. Each hole pair was progressively smaller in diameter, shorter and closer together As an example, the smallest hole pair included 0.40 mm diameter holes with a center-to-center separation of 0.127 cm and hole depths of 0.89 cm (Figure 5). Metrics evaluation focused

primarily on resolving the inside edge-to-inside edge separation on this smallest hole pair, which was 0.086 cm (Figure 6). The target was imaged in 4 locations within the field-of-view (center, left, right and top), thus providing some indication of the resolution in the periphery of the image as well as at the center.

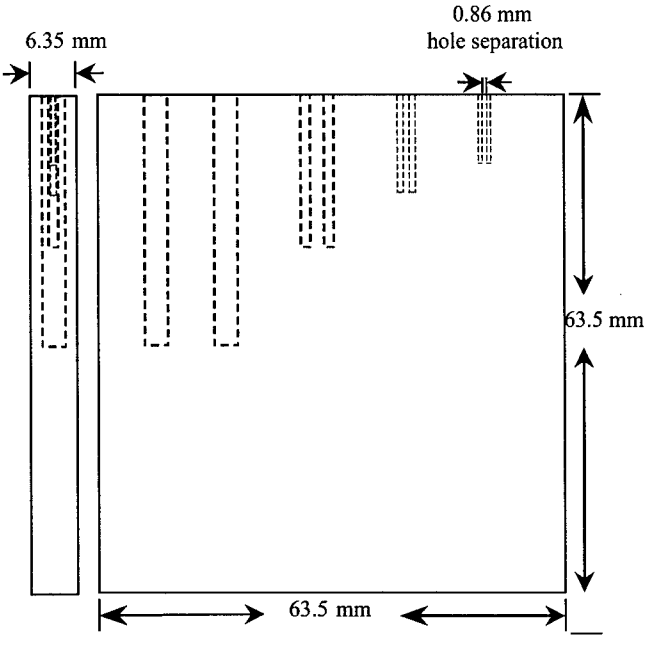

Fig. 5: Drawing of spatial resolution target

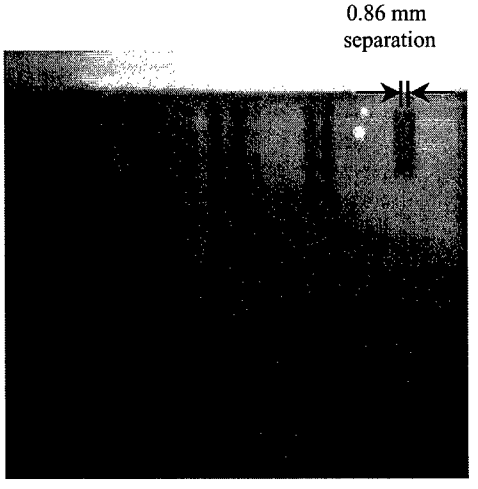

Fig. 6: DEI image of spatial resolution target

3.4 Contrast resolution

Contrast resolution is defined as the number of levels of gray per decibel (dB) of signal loss, where signal loss can include reflection and/or attenuation. Unfortunately, this was confounded a bit in resultant images since the DEI technology has inherent edge enhancement where tissue boundaries appear darker than the tissue on either side of the boundary. Thus, this definition only applied to a homogenous section of an object where diffractive energy was negligible.

A calibrated acoustic step wedge target (Figure 7) with known attenuation (Figure 8) was used to measure the contrast resolution of the DEI system. This target was placed in the focal plane at a specified distance from the transducer head, and the image was recorded. After normalizing the image to the background intensity the contrast resolution as defined above was computed. The normalized step wedge could be used also to make direct comparisons to the system MTF.

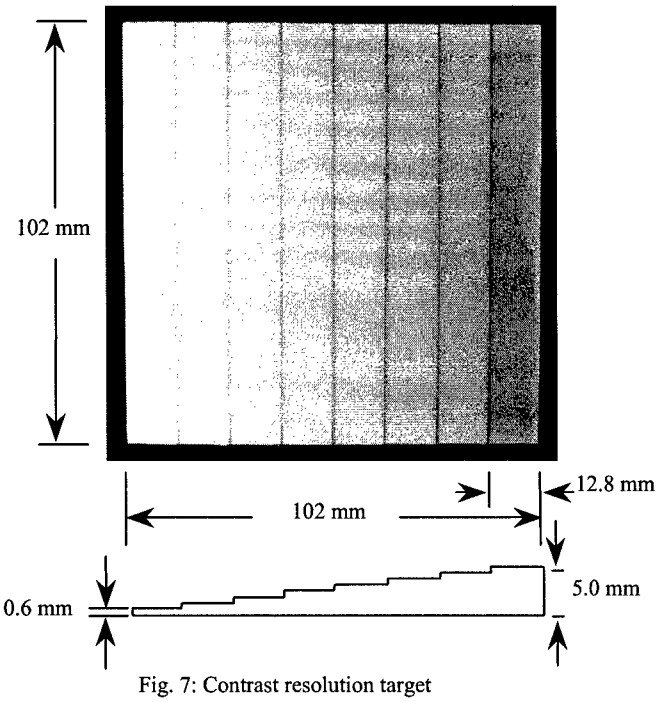

Fig. 7: Contrast resolution target

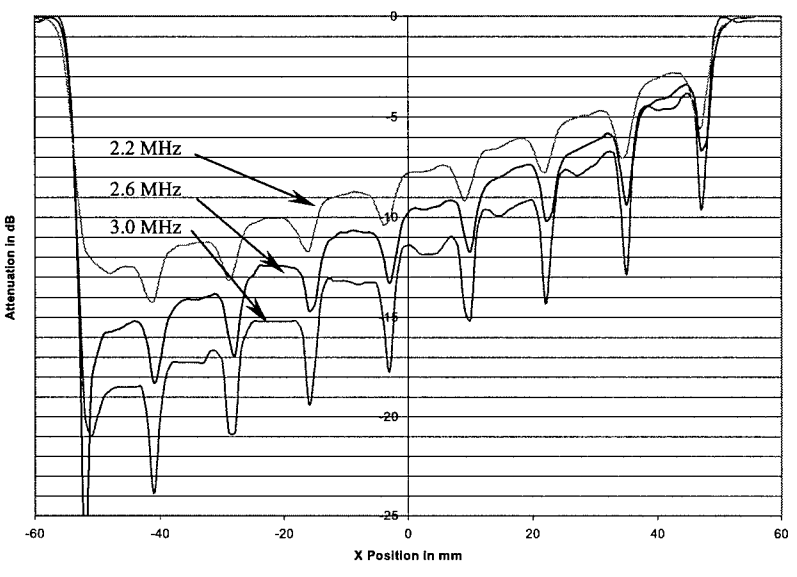

Fig. 8: Attenuation shown for three frequencies at each physical step in the contrast resolution target

3.5 Field uniformity

Field uniformity is another important metric. In the current DEI configuration this is determined by two parameters: the uniformity of the acoustic insonification, and the uniformity of the optical illumination. Measuring the acoustic insonification separately is a rather tedious task involving a hydrophone scanning apparatus that is difficult to implement in the current AVERA imaging device. Although measuring the illumination uniformity should be somewhat easier, this has not yet been done. The approach taken here was to perform simply pixel value statistics on a plain background image and track changes to the resulting values (e.g., mean, standard deviation, histogram profile). Figure 9 illustrates the output of this metric.

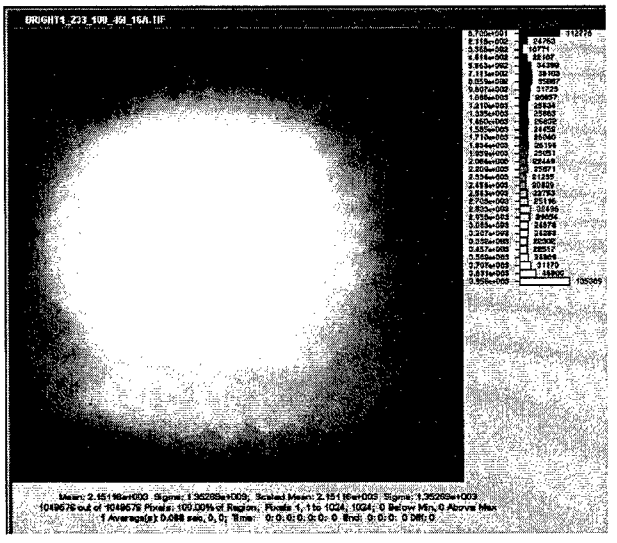

Fig. 9: Field uniformity

3.6 Minimum detection DEI system sensitivity was defined by the smallest detectable object. The approach taken to determine sensitivity was by defining detection limits using quantifiable targets. The sensitivity phantom used to determine DEI detection limits was fabricated using small, high contrast objects embedded in a phantom. The phantom substrate material approximated the acoustic properties of soft tissue (measured sound speeds and attenuation of 1495 m/sec and 0.95 dB/cm/MHz, respectively) and measured 5 cm in thickness along the sound path. The small, high contrast objects embedded in the phantom were sieved particles of hydroxyapitite crystals, simulating calcifications (Figure 10). Optical microscopy was used to verify sieved material sizes (Figure 11). The targets appear black against the homogeneous substrate material. The results show that DEI can begin to detect small, high contrast targets in the range of 0.2 mm at typical DEI breast imaging frequencies (i.e., frequency sweep from 2.4 to 3.0 MHz).

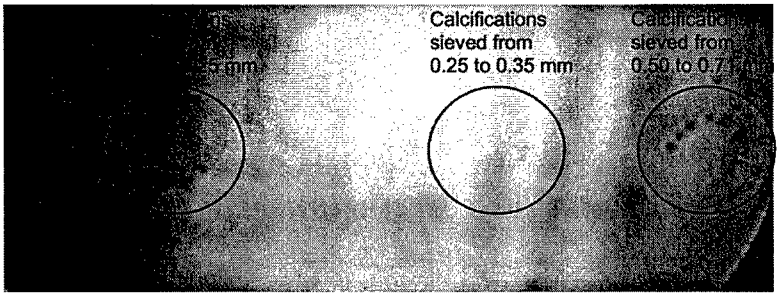

Fig. 10: Simulated calcifications embedded in breast phantom illustrating minimum detection

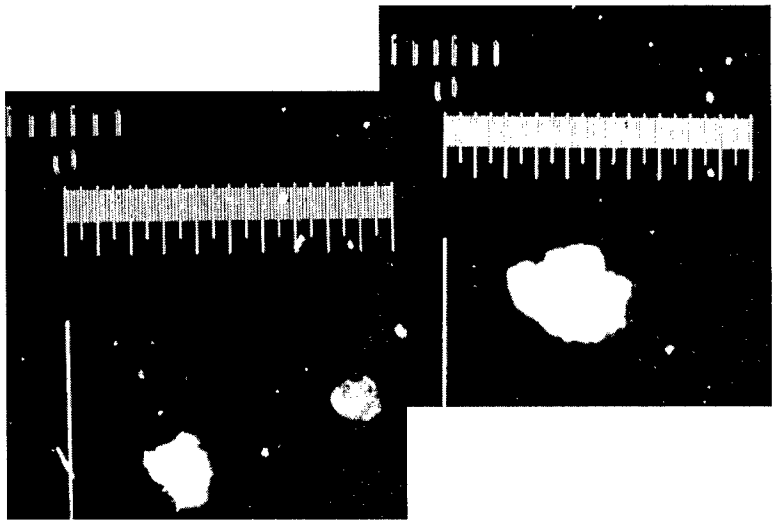

Fig. 11: Verification of simulated calcification target sizes using optical microscopy (maximum scale = 1mm)

4. DISCUSSION

ADI's metrics program was implemented successfully and has provided a standardized method for quantifying DEI system performance, tracking performance associated with specific system and component modifications, and correlating metrics results with changes in image quality. The obvious extension to the collection of metrics data using standard targets was the more subjective evaluation of the resulting clinical images. When metrics are taken to assess changes associated with system modifications, both pre-change and post-change clinical images were acquired and evaluated by clinical specialists. Figures 12 and 13 illustrate the impact that some of the system modifications have had on clinical image quality and how this more subjective validation can help drive system change decisions. The improvements shown in the images on the right in each set most notably included increases in the effective field-of-view, field uniformity, MTF, and spatial resolution. Clinical results were described as improved tissue edge definition, increased field-of-view, and better tissue visualization in the upper regions of the images. These improvements reflect changes primarily to the DEI system acoustic chain.

Several future activities are planned to improve both the accuracy, repeatability and ease with which data are collected, archived and analyzed. Anticipated activities include additional characterization of targets, development of fixtures to locate targets accurately in defined focal planes, automation of data collection and analysis, and improvement to the link between metrics data collection and clinical outcomes to drive future metrics program development.

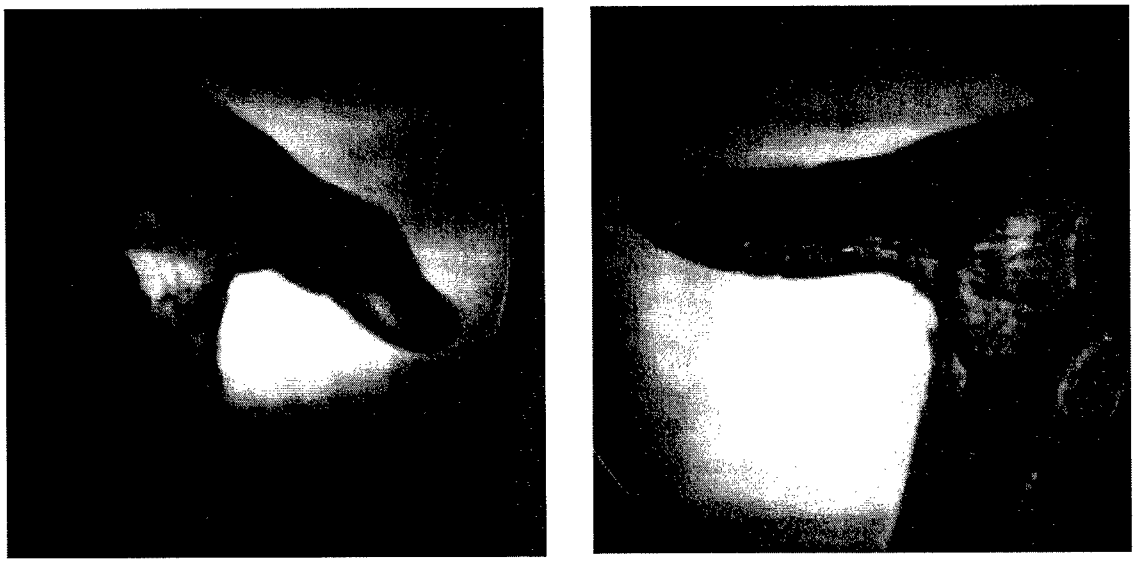

Fig. 12: Images of the thumb illustrating pre-image quality improvements (left image) and post-image quality improvements (right image) in the same subject

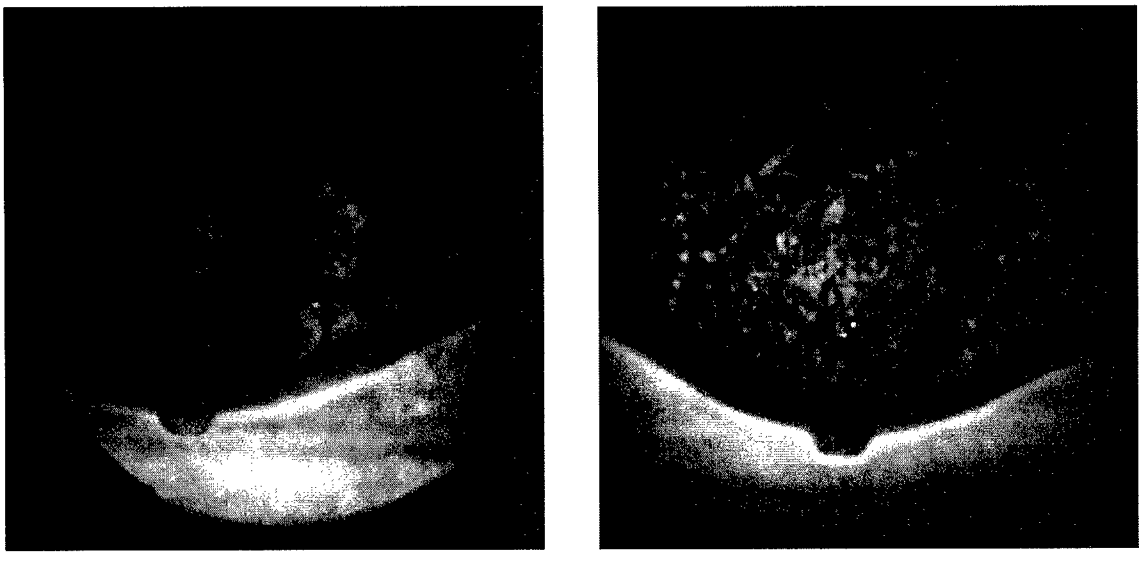

Fig. 13: Breast images of the same subject showing pre-image quality improvements (left image) and post-image quality improvements (right image)

ACKNOWLEDGEMENTS

ADI gratefully acknowledges support from the Department of Defense under Breast Cancer Research Program grant No. DAMD17-99-1-9053.

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Toward guided breast biopsy using Diffractive Energy Imaging

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ABSTRACT

Advanced Diagnostics, Inc. (ADI) has developed a technique using Diffractive Energy Imaging (DEI) to provide an accurate, non-ionizing method for continuously tracking biopsy needles. The method utilizes ultrasound to generate large field-of-view, high resolution, multi-planar images. Accurate, real-time biopsy guidance using DEI is possible by identifying the physical relationship between a lesion and a focal plane or image slice. The lesion is located by progressively focusing through the breast volume until the lesion is visualized with enough clarity to distinguish it from surrounding tissue. The selected focal plane identifies the lesion location along a medial-lateral axis through the breast. This plane is identified for the physician using a laser pointer to "paint" a line on the skin surface. Cartesian coordinates applied to the image slice define a location for surgical incision and needle entry along this focal plane. Maintaining the needle within the defined focal plane and tracking the needle in real-time on a high-resolution monitor ensures a direct line approach through the tissue to the targeted lesion. Data indicate that physicians experienced in biopsy but without prior DEI operational experience are successful in acquiring simulated targets embedded in biopsy phantoms.

Keywords: biopsy guidance, Diffractive Energy Imaging, acoustic holography, real-time biopsy

1. INTRODUCTION

Core needle breast biopsies are routinely performed using stereotactic mammography or free-hand reflective ultrasound guidance. Percutaneous core needle biopsies performed using stereotactic mammography guidance are typically lower in cost than excisional biopsies and result in less emotional trauma and physical scarring in patients.[1,2,3] The procedure, however, is time consuming and needle accuracy can be compromised with patient movement when real-time image guidance is not available. In addition, stereotactic breast biopsy devices are dedicated systems requiring significant hospital space. In free-hand ultrasound guidance, biopsy accuracy is highly dependent on operator experience and skill. Using this technique, the breast must be stabilized, the needle is maintained parallel to the imaging plane, and position confirmation is made viewing orthogonal planes.[4] Advanced Diagnostics, Inc. (ADI) has succeeded in developing an approach to core needle biopsy that utilizes Diffractive Energy Imaging (DEI)[5,6] and addresses many of the problems associated with traditional techniques.

2. METHODS

DEI is an imaging technology based upon sound and sound wave mechanics, but utilizing sound in a non-traditional fashion. While conventional ultrasound relies on the reflective properties of sound and is a pulsed wave technique, DEI uses a "through wave" technique that takes advantage of the diffractive properties of sound. The DEI image is formed by passing a coherent wave of sound through an object (Figure 1). The ultrasonic energy is absorbed, reflected, diffracted and refracted by anatomical structures, thus perturbing the transmitted wave in a manner unique to the internal anatomy. The summation of these perturbations in the transmitted wave is combined with an unperturbed reference wave in real-time to generate an acoustic hologram. A coherent light source is used to illuminate the hologram. Two-dimensional real-time digital images are then acquired using a high resolution CCD. Image slices acquired in sequence through an

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object can be used to generate a volumetric image set. Key to the creation of image slices is the acoustic lens combination that allows the operator to focus on selected planes of interest within the object, and scale regions of interest within a slice. DEI is particularly effective in imaging the breast; muscle, tendon and joint anatomy; and vascular structures where differentiation among soft tissue structures is important. The specific strengths of the DEI technology include: real time imaging, an automated multi-planar scanning paradigm, minimum operator dependency, and high spatial and contrast resolution. Other advantages include: no ionizing radiation, no painful compression during breast imaging, and DICOM compatible image formats that ensure smooth integration into Radiology information networks.

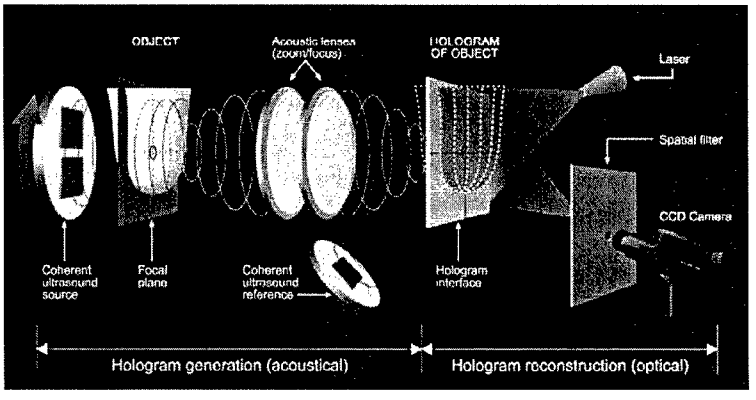

Fig. 1: Formation of the DEI image

2.1 DEI biopsy guidance design

ADI's initial focus has been to design, develop and produce a breast imaging system that incorporates breast biopsy guidance. The Avera, ADI's first breast imaging product, is illustrated in Figure 2. This system will accommodate a variety of commercially available handheld biopsy probes that are guided manually. To help direct the physician during biopsy, image information is provided to locate the lesion along the X and Y axes, and focal plane information is

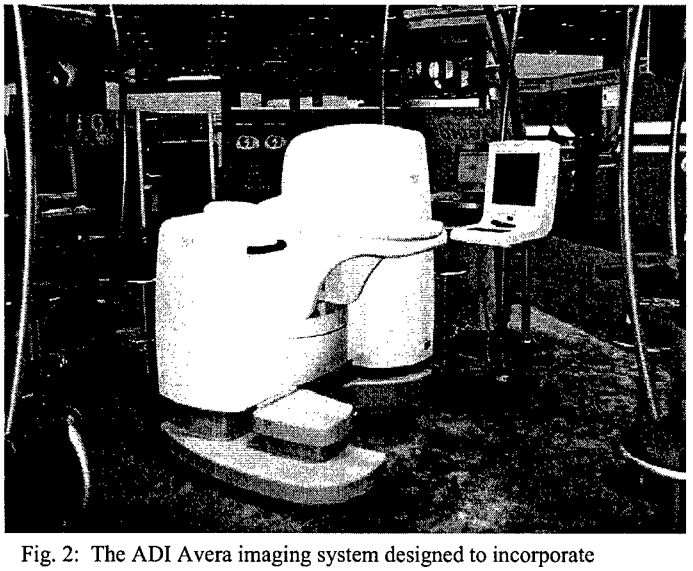

Fig. 2: The ADI Avera imaging system designed to incorporate breast biopsy image guidance

provided to locate the lesion along the Z axis. At this time, no mechanism is provided to constrain the probe along any axis of motion.

During the imaging procedure the patient lays prone on the patient table with the breast suspended through a hole, similar in configuration to a stereotactic breast biopsy table. The breast is lowered into a water bath for initial imaging, and is secured and immobilized using two vertical plates located medial and lateral to the breast. A plane wave of ultrasound energy, sweeping at frequencies from 2.5 MHz to 3.1 MHz, is transmitted through the vertical plates, water bath, and breast. A large field-of-view image of internal breast structure is produced. As the operator progressively focuses through the breast volume, the lesion will come into focus and an associated focal plane can be identified. The operator also centers the lesion in the field-of-view by incrementally moving the table in a patient superior-inferior and/or anterior-posterior direction. Once the lesion is centered in the field-of-view and in focus, the water is drained from the imaging tank and an access window is opened to provide either a superior or inferior dry approach to biopsy. This latter feature, shown in Figure 3, provides access for standard sterilization, incision and biopsy procedure. The breast remains immobilized by the vertical plates. Sound path continuity is maintained by fluid located external to the vertical plates and by continuous contact between the plates and the breast.

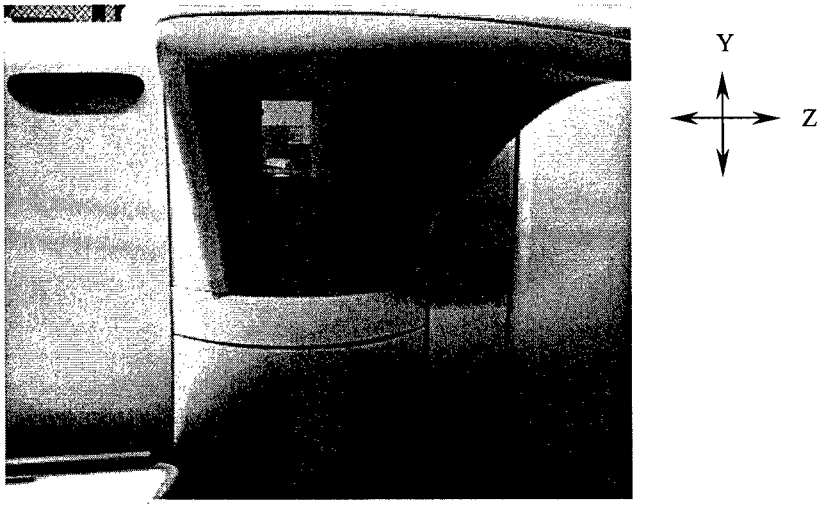

Fig. 3: Biopsy access window located below patient table

The DEI design objective was to provide the operator with accurate, real-time information to make a direct line approach to the targeted lesion. Knowledge of lesion location prior to needle insertion, projected point of entry at the skin surface, and real-time visualization of the needle during biopsy all help to establish the desired path from the skin to the targeted lesion. These cues are introduced to the physician using DEI approach guidance in combination with real-time needle visualization. Axial or Z coordinate lesion location is established once the operator identifies the focal plane of the lesion. Because the acoustic lenses are encoded, the relationship between lens position and focal plane is known. The GUI displays a focal plane value that corresponds to a Z location on a calibrated rail mounted at the open breast access window. A moveable laser pointer is mounted to this calibrated rail. The operator moves the laser pointer along the rail until the displayed focal plane value is achieved. When activated, the laser pointer "paints" a line at the skin surface indicating the desired plane of entry. While the relative vertical or Y-axis location of the lesion is known *a priori* from the image, information is provided to help the physician locate more accurately the incision point and needle entry at the skin. A fixed, calibrated scale is provided along the vertical edge of the image and corresponds to a scale mounted to the side of the patient tank. The operator reads the Y-axis position from the GUI and makes an incision at a corresponding Y-axis location on the breast in the designated focal plane. Penetration through the breast along the X-axis to the lesion is controlled by tracking the needle in real-time on the high resolution monitor.

2.2 Data collection procedure

A series of breast biopsy simulations was performed to determine the accuracy with which a subject could locate and biopsy targets visualized using DEI technology. Ten subjects were recruited. Five were physicians or residents with biopsy experience but no system operational experience, two were non-physicians with detailed system operational experience, one was a non-physician with clinical operational experience, and two were non-physicians with no system operational experience.

Gel phantoms with embedded peas were used as biopsy targets. Twenty rectangular gel phantoms were fabricated based upon a recipe designed to approximate the acoustic properties of soft tissue.[7] Each phantom measured approximately 11.4 cm long x 6.6 cm wide x 5.1cm deep. Five peas measuring between 6.0 mm and 10.0 mm were embedded into each phantom, each pea located at one of three predefined depths. Each phantom was numbered with the location of the embedded lesions noted. Sewing needles were used to simulate biopsy needles and measured 7.6 cm long with a tapered diameter from mid-shaft (0.9 mm) to tip (0.5 mm). Needles approximated 22 gauge (0.7 mm) aspiration needles in size and were used to represent a challenging biopsy scenario. Subjects were assigned two phantoms each and asked to perform ten separate biopsies.

As part of the biopsy procedure, each subject was given a demonstration of the technology. The first of two phantoms assigned to each subject was positioned in the patient tank and immobilized between the vertical, stabilization plates. Once the target was in focus and a focal plane was established, the calibrated laser sighting device was positioned to illuminate this focal plane at the phantom surface. The subject was instructed to perform the biopsy by maintaining the needle parallel to the focal plane and using real-time image information to direct the needle in both the X and Y-axes. The objective was to push the needle through the lesion as close to the physical center of the pea as possible while viewing the biopsy on the monitor. The first biopsy was performed as a practice trial. Each subject then performed nine additional biopsies at 3 different biopsy distances.

DEI images were acquired for each biopsy phantom following the completion of each series of 5 biopsies (Figure 4). Needles were left in place after each procedure and each phantom was imaged using X-ray mammography. Films were obtained for both the X-Y and Y-Z planes and were used to measure the relative needle and lesion positions (Figures 5a and 5b). To identify the position of each of the 5 needles it was necessary to cut Y-Z planar slices, isolating the needles for image review (Figure 5b). These films provided a method for determining the accuracy of each biopsy in the image plane and along the Z axis.

Fig. 4: DEI image showing needles (representing five biopsy trials) targeting embedded peas in the X-Y plane of a single gel phantom.

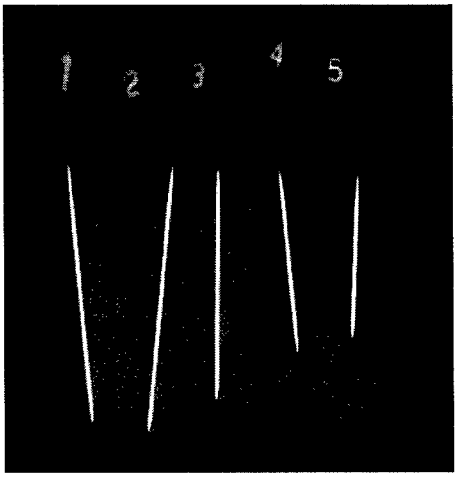

Fig. 5a: X-ray image of biopsy phantom showing needle accuracy in X-Y plane.

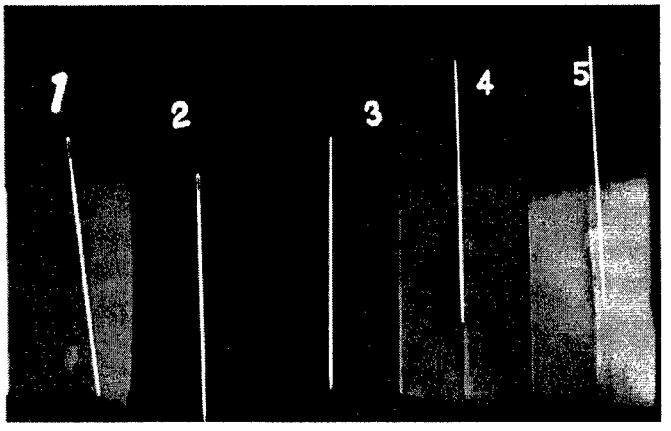

Fig. 5b: X-ray image of slices through biopsy phantom showing needle positions in Y-Z plane.

3. SUMMARY DATA

Measurements taken from the X-ray films included: target (pea) diameter; distance from the target to the phantom surface; distance from the needle to both the closest edge and center of the target in the X-Y plane; distance from the needle to the lesion edge along the Z axis at the target; distance from the needle to the lesion edge projected at the surface; and the angle of the needle from the perpendicular to the surface in both planes.

Measured target diameters ranged from 6.0 mm to 10.0 mm with a mean diameter of 8.2 mm (SD=0.8). The biopsy distance (i.e., surface of the phantom to the near edge of the target) for each of the embedded targets was measured. The three distances were grouped into a short, medium and long biopsy distance. The shortest distance averaged 1.0 mm (SD=0.3); the medium distance averaged 2.8 mm (SD=0.4) and the longest distance averaged 4.7 mm (SD=0.2).

Biopsy data by group are summarized in Table 1. Group 1 represents non-physicians with detailed DEI system operational experience, Group 2 corresponds to those subjects with biopsy training and experience but with no DEI system operational experience, Group 3 represents non-physicians with neither biopsy nor DEI system operational experience, and Group 4 represents a non-physician with DEI clinical operational experience.

Table 1: Biopsy Results

Group No.*	No. of Subj	Biopsy Attempts	Successful biopsies in X-Y		Ave dist- needle to lesion center	Successful biopsies in Z		Z misses due to needle angle			Z misses due to focus		
			(#)	(%)	(mm)	(#)	(%)	(#)	(%)	ave angle (deg)	(#)	(%)	ave dist (mm)
1	2	18	18	100	0.83	17	94	0	0	2.1	1	100	1.00
2	5	45	45	100	0.81	33	73	2	17	2.5	10	83	4.33
3	2	18	18	100	0.83	9	50	2	22	3.3	7	78	2.44
4	1	9	9	100	1.00	2	22	1	14	5.7	6	86	2.79
Total	10	90	90	100	0.84	61	68	5	17	2.9	24	83	3.26

*Group 1- non-physicians with no biopsy experience; extensive DEI system operational experience
Group 2- physicians or residents with biopsy experience and training; no DEI system operational experience
Group 3- non-physicians; no DEI system operational experience
Group 4- non-physician; DEI clinical operational experience

4. RESULTS

One hundred biopsies were performed. The first biopsy performed by each subject was considered a training biopsy and was not analyzed. The remaining 90 biopsies, 9 completed by each subject, were analyzed to determine needle accuracy in both the X-Y and Y-Z planes.

Each subject was instructed to hit the lesion as close to its physical center as possible. Of the 90 biopsies performed, there were no targets missed in the image plane (X-Y plane). These data show that the average distance from the needle to the target center for all cases was one millimeter or less. Subjects indicated that biopsy execution in this plane was extremely straightforward, requiring little skill.

Data reveal that targeting simulated lesions in the Z axis proved to be more challenging, especially for those with no biopsy experience and no DEI system operational experience. To attain the target in the Z axis, it was important for the subject to focus on the target accurately and establish the correct focal plane. Once the laser sighting device was set to physically identify the focal plane, it was important to maintain the needle parallel to this focal plane during the biopsy attempt. Biopsy misses along the Z axis were analyzed for those experienced and inexperienced in both biopsy and DEI system operations. The data show that those experienced in DEI system operations but with no biopsy training and experience had the highest success rate, hitting the targets in 94% of the attempts. The percentage of successful biopsies for physicians and residents with biopsy training and experience but with no DEI system operational experience was 73%. The percentage of successful biopsies dropped considerably for those with no biopsy training, no biopsy experience, and limited or no DEI system operational experience.

The Z axis misses were further investigated to determine whether they resulted from: 1) accurate needle location in the focal plane but improper needle angle to intersect the target, or 2) inaccurate focal plane identification, large enough so that the target would have been missed even with proper needle angle. The data show that 17% of the misses in the Z axis resulted from improper needle angle when the focal plane was correctly located. The majority of the misses in the Z axis (83%) resulted from improper focus, presenting an error distance in the focal plane great enough such that the target was missed with proper needle angle.

These limited data indicate that tracking a biopsy needle in the DEI image plane may present an intuitive approach for physicians performing core needle biopsies. However, the data also indicate that the challenge to accurate biopsy using the DEI technology is in attaining the target successfully in the Y-Z plane. To ensure accuracy along the Z axis, the physician must first ensure that the lesion is in focus. Then, once the focal plane is accurately identified, the physician must maintain the needle in the identified focal plane. The results suggest that more experienced operators can identify the focal plane more accurately. This, of course, suggests that training and experience will become an important element to biopsy accuracy when using this system. These results also suggest that when the subject's attention is divided between the monitor and the patient there may be software and/or hardware design considerations that could assist the physician in locating the focal plane and maintaining the needle within that focal plane more easily. ADI intends to concentrate on optimizing the DEI imaging system for the non-experienced user to increase the ease of use and the accuracy of biopsies.

5. CONCLUSIONS

For many women minimally invasive needle biopsies have become an important alternative to more invasive, open surgical biopsies. Needle biopsies have been shown to be less expensive than surgical biopsies and less invasive. However, using traditional methods, physicians still cannot track biopsy needles continuously and easily in real-time with desired image clarity. Preliminary biopsy results using the DEI medical imaging system show promise in accurately targeting simulated lesions in biopsy phantoms. Reactions from physicians indicate an intuitive navigation process within breast phantoms and image clarity that has not been obtained with other real-time medical imaging technologies. Additional work in this area will address the impact of training and biopsy experience on needle placement accuracy and the need for software or hardware enhancements that will assist the physician in improving biopsy accuracy along the Z axis.

ACKNOWLEDGEMENTS

ADI gratefully acknowledges support from the Department of Defense under Breast Cancer Research Program grant No. DAMD17-99-1-9053.

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Diffractive Ultrasound Descriptors for Breast Imaging

a guide to image interpretation

1.0 INTRODUCTION

Descriptions of breast masses and their features have evolved over many years. This evolution has come primarily through correlation of morphologic parameters with the clinical course of breast disease, and through the assessment of mammographic and conventional ultrasound findings. To encourage consistency, mammography findings and definitions have been integrated as part of the American College of Radiology Breast Imaging Reporting and Data system (BIRADS™).[1] The BIRADS™ lexicon is intended, in part, to help standardize the descriptive language used to summarize mammographic findings. Features describing these findings are illustrated using line drawings and sample images. Many of these features are applicable to the development of descriptors for Diffractive Ultrasound (DUS), an emerging breast imaging technology developed by Advanced Imaging Technologies, Inc. (AIT). The purpose of this paper is to provide an initial set of DUS descriptors based, in part, upon the BIRADS™ lexicon. The emphasis will be on initial descriptors for breast orientation and mass location; mass features including size, shape, margin, density, and internal architecture; and breast composition. These descriptors will be used to improve interpretive skills as DUS image data are collected, reviewed, and compared, and over time will be modified as appropriate.

While DUS technology is based upon sound and sound wave mechanics, researchers often find stronger correspondence between breast mass features using mammography and DUS than between DUS and conventional ultrasound. This is likely due to the large fields of view and similar scan plane orientations provided by both mammography and DUS. In addition, the diffractive and absorptive properties of tissue when exposed to DUS yield strong breast mass margin, density and textural features that have been interpreted in much the same fashion as in mammography. While DUS is a unique imaging modality that will likely require many of its own descriptors to articulate image findings accurately and consistently, the correlative strengths with mammography encourage the use of portions of the BIRADS™ lexicon during initial development of DUS descriptors.

2.0 METHOD

DUS is categorized as a new imaging modality because of its non-traditional use of sound. While conventional ultrasound relies on the reflective properties of sound and is a pulsed wave technique, DUS uses a "through wave" technique that takes advantage of the diffractive properties of sound. A DUS image is formed by passing a coherent wave of sound through an object (Figure 1), where ultrasonic energy is absorbed, reflected, diffracted and refracted by anatomical structures. The resulting perturbed wave is unique to the internal anatomy. The summation of these perturbations in the transmitted wave is combined with an unperturbed reference wave in real-time to generate an acoustic hologram. A coherent light source is used to illuminate the hologram. Two-dimensional real-time digital images are then acquired using a high resolution CCD. Image slices acquired in sequence through an object can be used to generate a volumetric image set. Key to the creation of image slices is the acoustic lens combination that allows the operator to focus on selected planes of interest within the object, and scale regions of interest within a slice. DUS is particularly effective in imaging the breast; muscle, tendon and

joint anatomy; and vascular structures where differentiation among soft tissue structures is important. The specific strengths of the DUS technology include: real time imaging, an automated multi-planar scanning paradigm, minimum operator dependency, and high spatial and contrast resolution. Other advantages include: no ionizing radiation, minimal compression during breast imaging, and DICOM compatible image formats that ensure smooth integration into Radiology information networks.

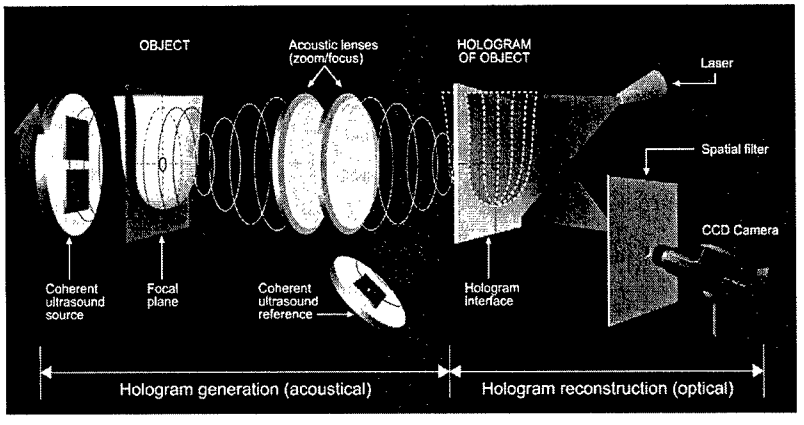

Fig. 1. Formation of the DUS image

Examinations are performed with the patient lying prone on a table and the target breast suspended in a water bath. The breast is secured and immobilized using two vertical plates located medial and lateral to the breast. A plane wave of ultrasound is transmitted through the vertical plates, water bath and breast producing a large field of view image of internal breast structure. As the operator progressively focuses through the breast volume, specific structure within a focal plane or slice will move into and out of focus. An autoscan is a series of these slices. The operator can obtain an autoscan of the entire breast, where slices can be acquired in 1 mm increments or larger, or an autoscan of a selected region of interest (e.g., through a mass). In addition, a systematic approach to patient examinations and imaging technique, product release and system maintenance with appropriate quality controls, and training for skilled technologists have been implemented to ensure consistency and high quality in image data collection.

3.0 APPROACH

3.1 Breast Orientation and Mass Location

Orientation of the breast and accurate location of structures within the breast using DUS is facilitated by the large field of view projections, image labels, and the identification of focal plane slices in positional graphics. During image acquisition, the on-screen image displays the breast as if the source transducers represented a camera taking a picture that is then projected on the computer monitor. This generates an image where the subareolar region is located in the lower portion of the image corresponding to its position in the patient tank, and the posterior breast is located at the top of the image. The superior and inferior breast regions correspond to image right or left, respectively. Labels are provided for added clarification. Upon study closure, images can be sent to an AIT workstation for review and processing. In this case, a DUS image display

protocol is implemented which rotates the image into a standard mammographic display format (Figure 2).

As the operator focuses through the breast, the focal plane is identified using a positional graphic display. The graphic illustrates either left (L) or right (R) breast, as appropriate, and provides a line representing the focal plane position. The line moves as the focal plane is moved, which helps identify the imaging plane in a medial or lateral direction. This orientation scheme and labeling help to locate a mass that can be described using numbers on a clock face as shown in Figure 3.

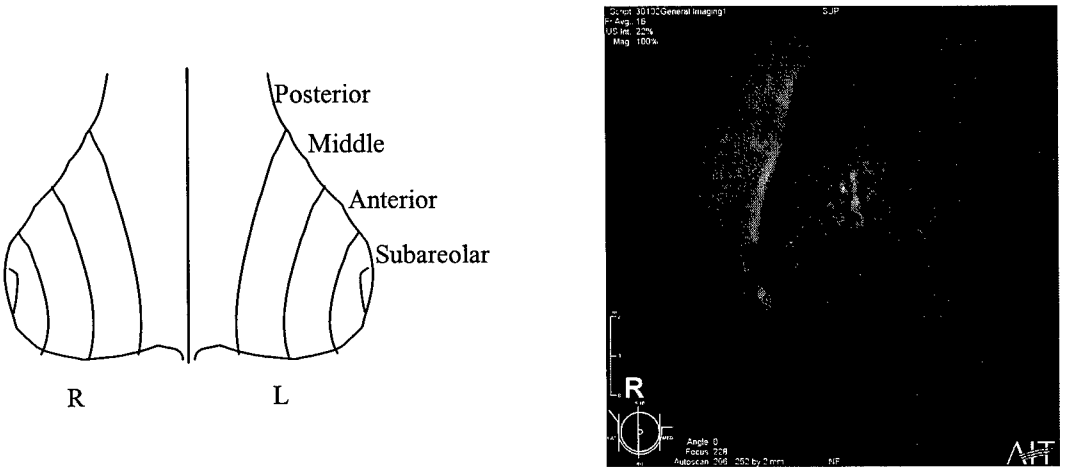

Figure 2. Location descriptors are illustrated in a sample DUS image. Reference to Right breast (R) and superior and inferior locations are given along with system settings. Correspondence to the drawing at the right can be made for different locations within the right breast.

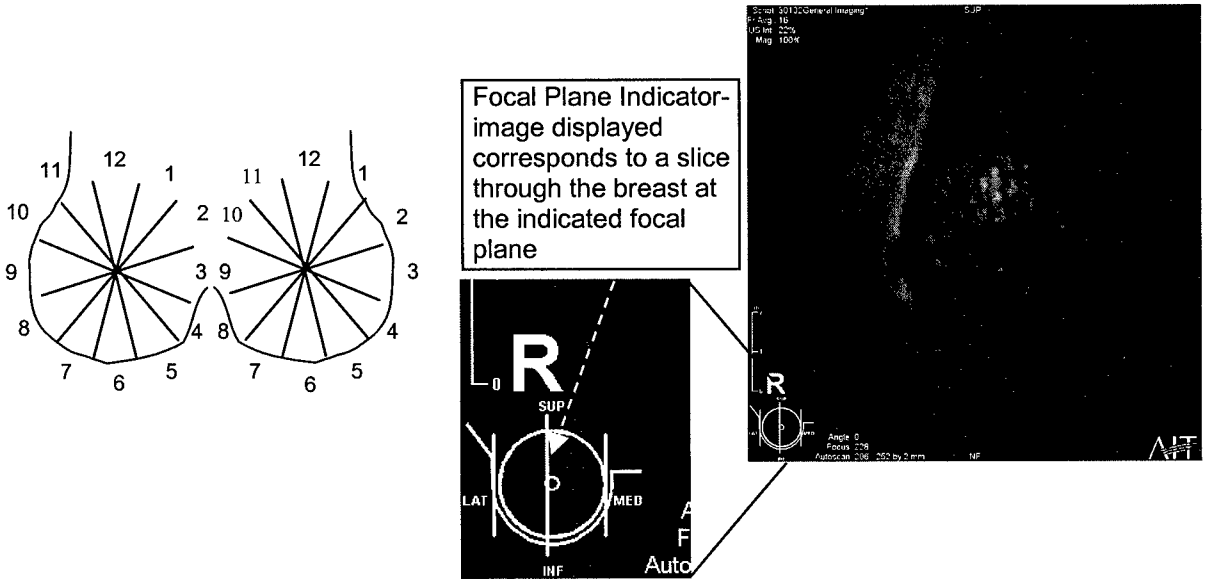

Figure 3. AIT positional graphic illustrates location of focal plane position in current image providing information for mass location using numbers on clock face shown at left.

3.2 Mass Features

3.2.1 Size. Mass size is determined through use of an on-screen graphic displaying a calibrated scale and, in a future software release, as a measurement tool accessible on the acquisition and review workstations. Linear and area measurement tools will be provided with graphic overlays embedded in selected images.

3.2.1 Shape. The shape of a mass seen on DUS can be categorized as round, oval, lobulated or irregular (Figure 4). The round mass is characterized as spherical, while the oval mass is elliptical. The lobulated mass is characterized as having multiple lobes or undulations, and the irregular shaped mass is one that cannot be described using any of the previous terms.

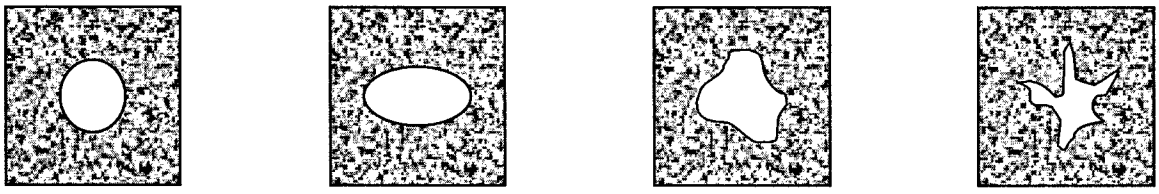

Figure 4. Descriptors for mass shapes

3.2.2 Margins. Margins of a mass as observed using mammography are major determinants of mass status (i.e., benign versus malignant).[2] Likewise, most notable among DUS properties is the ability to generate images that emphasize tissue boundaries. The resulting edge definition enhancement is expected to be a major contributor to mass categorization and interpretation. Following the BIRADS™ lexicon, DUS mass margin descriptors will include circumscribed, microlobulated, indistinct, obscured and spiculated (Figure 5).

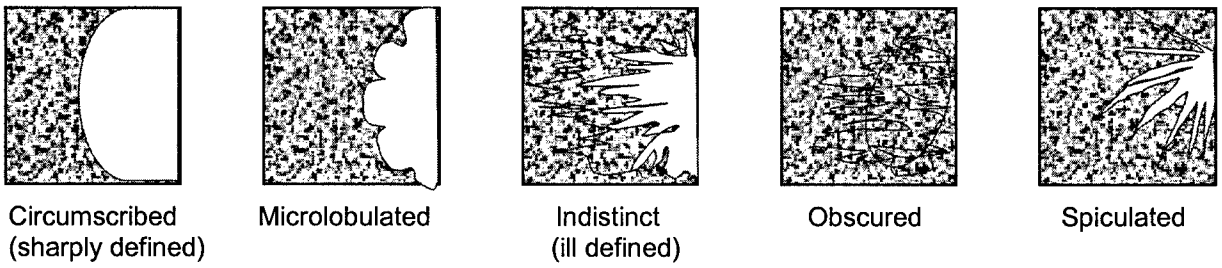

Figure 5. Descriptors for mass margins

3.2.3 Density. The density of a mass as observed using DUS is directly related to sound transmission, with denser masses generally absorbing more sound (i.e., less sound transmitted to the detector), and thus appearing darker relative to surrounding normal tissue. It is important to note that tissue density in DUS as discerned through grayscale values is relative to both the intensity of the sound source and the appearance of these tissues relative to surrounding tissue. In combination with other DUS descriptors, relative tissue density is likely to be a powerful predictor of mass status. It should also be noted that grayscale associated with tissue density in DUS is inverted when compared to mammography; as tissue density increases in DUS imaging, masses will appear increasingly dark. DUS descriptors proposed for use in categorizing tissue

density include high (sono-opaque), equal (isodense) and low (sono-transmissive) and are illustrated in Figure 6.

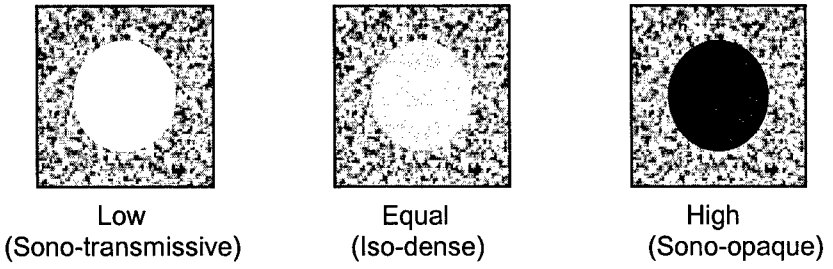

Figure 6. Descriptors for density of a mass

3.2.4 Internal Architecture. The internal architecture of a mass can be categorized as homogeneous or heterogenous (Figure 7), and is associated with the amount of DUS diffraction, indicating a relative amount of internal structure. Septations that produce visible separations among tissues also provide diagnostic value and are considered in this category. It should be noted that DUS does not generate isolated or discrete focal planes but rather has a depth of field that incorporates out-of-focus information on either side of a specified focal plane. Because the larger focal zone can incorporate information beyond the confines of a mass, it can be difficult to distinguish tissue that is internal to a mass from that which may reside outside of the mass but still within the focal zone. AIT continues to pursue system enhancements to isolate information within a selected focal plane, which may facilitate interpretation of internal mass architectures.

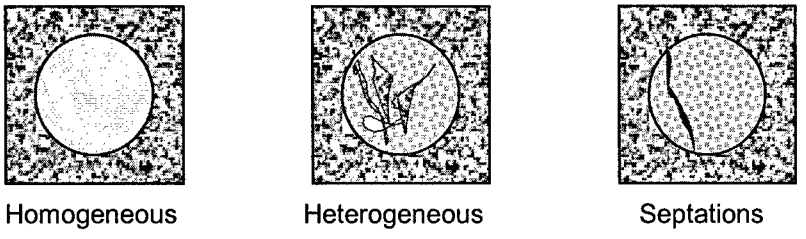

Figure 7. Descriptors for internal architecture of a mass

3.3 Architectural Distortion

An architectural distortion is described as tissue that is distorted, which may include spiculations that radiate from a point with no apparent defined mass, or a focal retraction or distortion of the edge of the parenchyma (Figure 8).

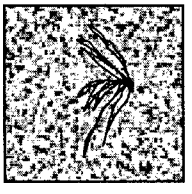

Figure 8. Architectural distortion

3.4 Breast Composition

Breast composition is a succinct description of the overall composition of the breast. In mammography the descriptors include primarily fatty, scattered fibroglandular, heterogeneously dense and extremely dense. These descriptors alert the physician to those patients where detection of masses may be difficult due to radiographically dense breast tissue. In a review of DUS images of both extremely dense and primarily fatty, the extremes in the existing breast composition range, the overall composition differences are not immediately obvious. It has been noted, however, that DUS sound intensities used are generally higher to achieve sound transmission in women with increased tissue densities. Also, with DUS strength in diffraction, it is expected that dense breast tissue will diffract more, and thus, more structure will be present in images of a breast composed primarily of denser tissue. This has been found to be generally true. Figures 9 and 10 illustrate a typical comparison between fatty and dense breast tissue.

Additional work may reveal that describing various breast compositions is not needed in DUS, if indeed all breast compositions can be imaged adequately without loss of image fidelity. However, until that hypothesis has been adequately researched and proven, descriptors for breast composition will be implemented. At this time, the proposed descriptors will divide breast composition by the degree of diffractive information observed. Terms proposed are low, medium and high diffraction, corresponding to fatty, scattered to heterogeneously dense, and extremely dense.

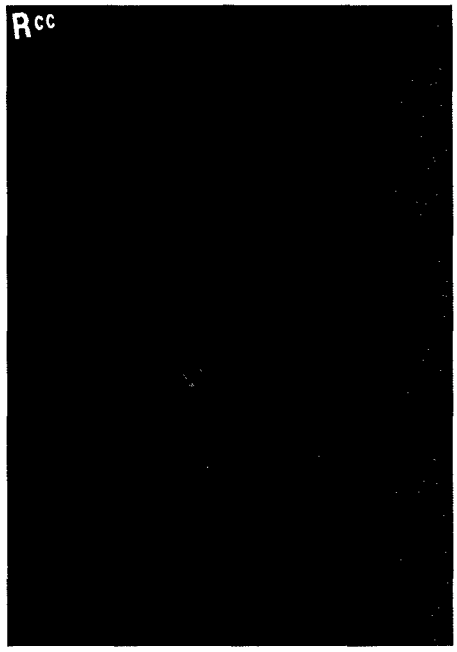

Figure 9a. Mammogram of normal subject with fatty breast composition (DUS image of same subject shown in Figure 9b)

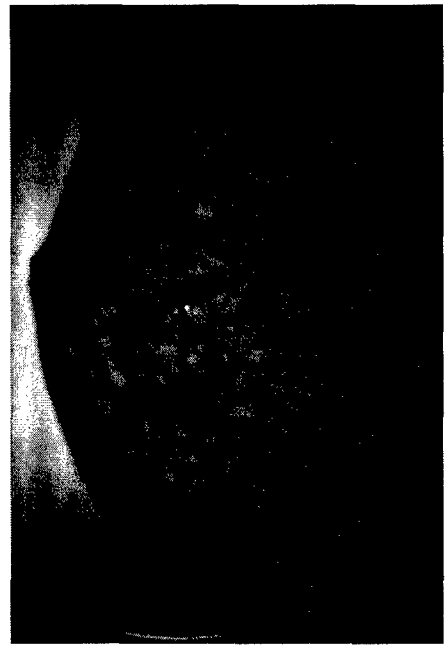

Figure 9b. DUS image of normal subject with fatty breast composition (Mammogram of same subject shown in Figure 9a)

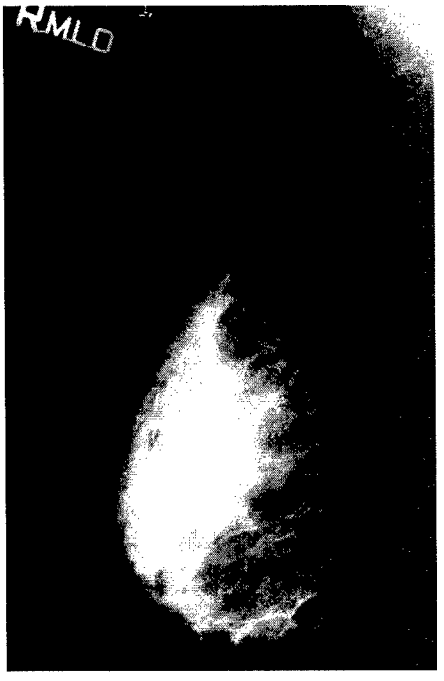

Figure 10a. Mammogram of normal subject with extremely dense breast composition (DUS image of same subject shown in Figure 10b)

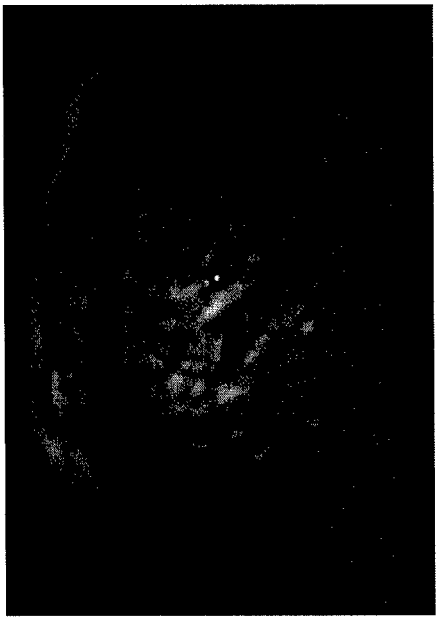

Figure 10b. DUS image of normal subject with extremely dense breast composition (Mammogram of same subject shown in Figure 10a)

4.0 APPLICATIONS USING PROPOSED DUS DESCRIPTORS

4.1 Benign Solid Masses

DUS images show benign solid masses as generally more *iso-dense* (equal density) relative to surrounding tissue with some masses showing somewhat more *sono-opaque* (high density). It is expected that margins and shapes will be consistent with that shown in mammography and conventional ultrasound, for example: oval shapes, large lobulations, wider in the lateral dimension than tall in the anterior-posterior dimension, and no strong indicators associated with malignant solid masses.[3]

Figure 11 illustrates several fibroadenomas. In the first two cases, the internal architecture is *heterogeneous*, shape is *oval* and margins are partially *circumscribed* with some portions *obscured* or *indistinct*. In the third case, the shape is *oval*, but the margins are *indistinct*. Most cases appear to be *iso-dense* relative to surrounding tissue.

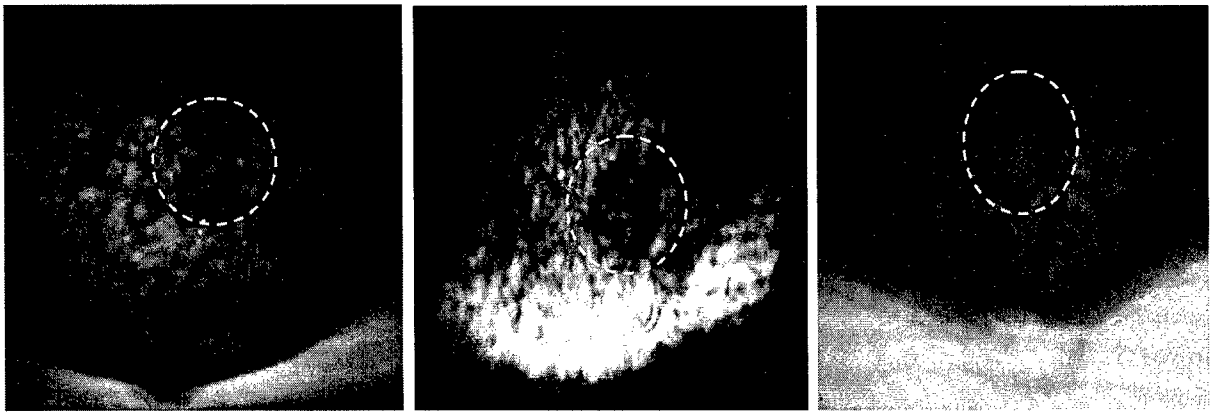

Figure 11. Fibroadenomas shown in three different women. Frame A shows a 2.0 cm oval mass located in the middle breast of a predominantly fatty breast of a 47 year old female. Margins are partially circumscribed with septations present. Frame B shows an oval shaped mass in a 40 year old female with heterogeneously dense breast composition. Frame C shows an oval mass with indistinct margins in a heterogeneously dense breast of a 37 year old female.

4.2 Malignant Solid Masses

Malignant masses show invasive characteristics primarily in size, shape, and internal architecture. Key features include *spiculated* capsules, taller (anterior-posterior dimension) than wide (medial-lateral dimension), *irregular* margins, branching patterns, *microlobulations*, and *sono-opacity* (high density).[3]

Figure 12 illustrates several carcinomas. These cases illustrate *irregular* shapes, *microlobulated* and *spiculated* margins, *sono-opaque* densities relative to surrounding tissue which are felt to be important features in DUS when describing malignant solid masses. These cases reveal apparent involvement with the surrounding tissue.

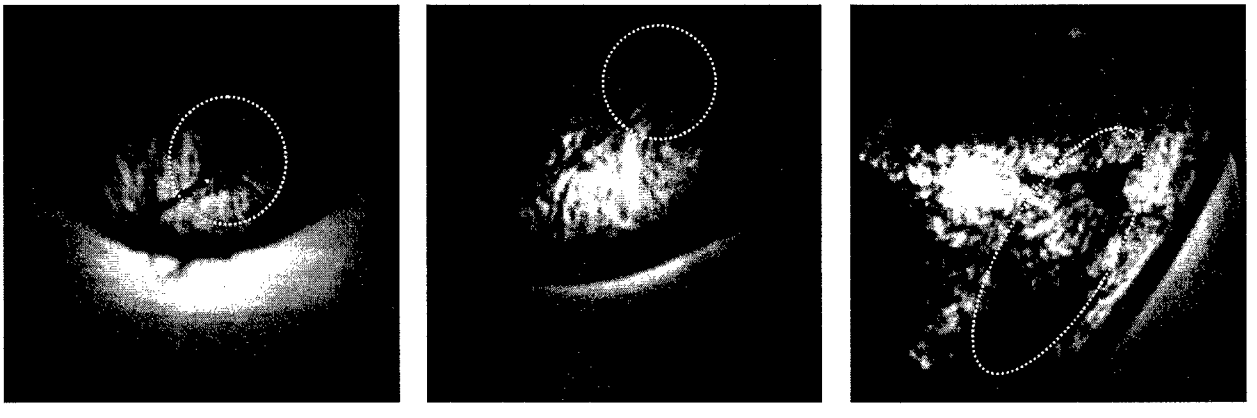

Figure 12. Three malignant solid masses in three different women. Frame A shows an adenocarcinoma in a 56 year old female. Frame B shows an infiltrating ductal carcinoma in the upper outer quadrant of a 73 year old female. Frame C shows an invasive adenocarcinoma with lobular and ductal features in a 64 year old female. All three cases show heterogeneously dense breast composition.

4.3 Simple Cysts

DUS clinical imaging experience shows simple cysts as generally more *sono-transmissive* (low density) than other masses or surrounding normal tissue. Many of the simple cysts also show increased internal *homogeneity*, likely indicating a more fluidic content. In addition, simple cysts

are often more *round* in shape. In some cases, the margins are *circumscribed* with diffractive properties defining thin encapsulations typical of simple cysts.

Figure 13 illustrates simple cysts in two subjects. The first case shows several 0.5cm cysts associated with a ductal structure in the anterior breast of a 39 year-old female. These smaller cysts show as *sono-transmissive* with more internal *homogenous* content and are fairly *round* in shape. Margins are rather *indistinct*. The second case shows a larger cyst located in the upper outer quadrant of a 50 year-old female. This cyst is *iso-dense* compared to surrounding fatty subcutaneous areas, *round*, and *circumscribed.* This second case raises the question of whether the dark boundaries are contiguous with *spiculations* or margins of adjacent structures. The autoscan becomes important in defining boundaries in these and adjacent structures.

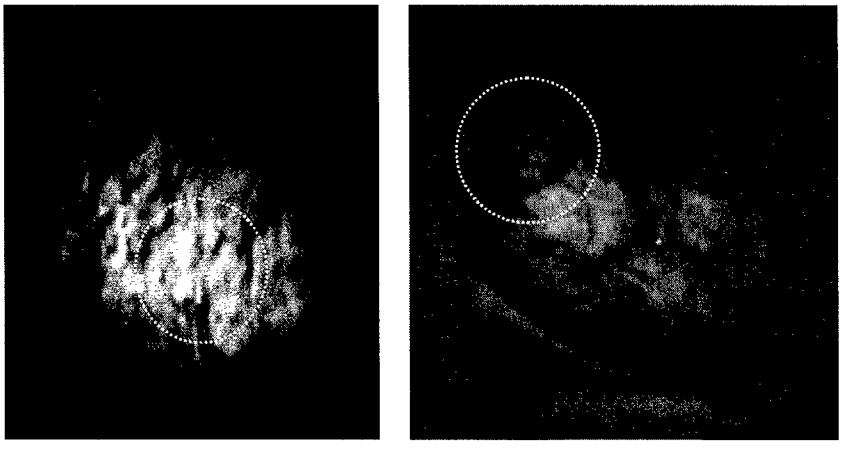

Figure 13. Simple cysts as imaged with DUS. Frame A shows several 0.5cm cysts associated with ductal structure in the anterior breast of a 39 year-old-female. Frame B shows a larger cyst located in the upper outer quadrant of a 50 year-old female.

4.4 Complex Cysts

As a complex cyst becomes more debris-filled the expectation would be to see more internal *heterogeneity* associated with this increase in internal viscous content. In addition, the expectation would be to see differences consistent with physical tissue characteristics of complex cysts, namely: increased numbers of thin and thick internal *septations*; more concavity and convexity to the wall structures; and often increased thickness of wall structures. These structural differences and the extent of heterogeneity may help in determining the consistency of cyst content, aiding future diagnostics. Figure 14 illustrates a cluster of 1-2 cm simple and complex cysts in a 38 year-old female. Note the *heterogeneity* of the internal structure, internal *septations*, *circumscribed* margins, and both convexity and concavity of wall structures. In addition, wall thicknesses are slightly increased and density is more *iso-dense*.

Additional work is required to evaluate how the content and compressibility of cysts effect the ability of DUS to easily identify these structures. It is suspected that a cyst compressed to a thickness smaller than the focal depth may prove more difficult to image. This is because the focal zone or image content would contain structure in front of and in back of the cyst rather than only the internal content of the cyst itself. These concerns are being addressed through research with clinical partners.

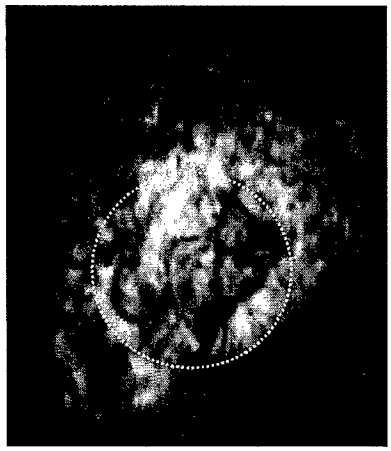

Figure 14. A cluster of 1-2cm simple and complex cysts imaged in a 38 year-old female.

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2. D'Orsi, C.J and D.B. Kopans. "Mammographic Feature Analysis." Seminars in Roentgenology, vol 28 (3), July 1993, pp. 204-230.
3. Rapp, C.L. "Sonography of the Breast." Official Proceedings of the Society of Diagnostic Medical Sonography's 17th Annual Conference, Dallas, TX, Sept 14-17, 2000, pp. 57-67.

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REPLY TO
ATTENTION OF

MCMR-RMI-S (70-1y) 15 May 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

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PHYLIS M. RINEHART
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